

Review Article

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Treating infertility: current affairs of cross-border reproductive care

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Abstract: Infertility patients are willing to travel abroad to receive the medical treatment of choice. A 2010 study reported that approximately 25,000 couples travel abroad annually seeking infertility treatment. The purpose of this review is to analyze the criteria and risks related to cross-border reproductive care (CBRC) from the perspective of the patients and explore the issues raised regarding the country of origin and the destination country. A computerized search was performed in PubMed employing respective keywords. The total number of published articles provided by our PubMed search was 1905. Criteria for selecting the destination country include: the economic status, legislation, quality of care and anonymity. Despite the fact that CBRC is becoming a familiar concept, it raises concerns for the practitioner and issues of a social and bioethical nature. Most of them stem from the fact that health care acquires a commercialization aspect. Medical tourism entails several risks, such as misconceptions regarding the destination country, and legal issues arising

from differences in the judiciary systems. Larger studies evaluating all aspects of CBRC are imperative. Quality assurance, a consensus and a common platform of practice, along with a system of international governance based on human rights, are a necessity for CBRC patients.

Keywords: CBRC; Risks; Bioethics; ART

1 Introduction

According to the World Health Organization (WHO), infertility is defined as a disorder of the reproductive system. Inquiring about treatment options in foreign countries is one of the main strategies couples choose to pursue. This process has been described as “medical tourism” [1]. Despite the fact that this term is commonly used, it has not been fully adopted by the scientific community. Terms such as “medical journeys”, “health traveler’s transnational health care” or “cross-border care” describe the phenomenon in a clear and elaborate fashion. These terms are preferred by most scientists, since the health-care factor is highlighted as the main motivation of the patients [2]. These terms refer to procedures that patients may be submitted to, such as in-vitro fertilization (IVF), oocyte and sperm donation, surrogacy, and preimplantation genetic diagnosis (PGD) [3].

The basic axis of the phenomenon of cross-border reproductive care (CBRC) revolves around ease of obtaining information on the internet regarding the different techniques available in foreign countries and ability to travel to any place that provides the medical care of choice [4] (UK). Beyond that, patients combine their journey in the context of CBRC with a holiday. The touristic value and strength of the destination country may play an important role [5]. The positive effect on the patients’ psychological state achieved by pairing treatment with recreation has earned CBRC a true standing as a trend that is studied and promoted within the medical community [5].

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It is understandable that CBRC is related to economic, legal, social, psychological and bioethical issues. The fact that approximately 20,000 to 25,000 couples annually travel abroad seeking infertility treatment [6] renders this study timely and important. The purpose of this work is to analyze these factors by examining particularly the concerns that arise during the relocation of CBRC patients to a foreign country to enjoy the benefits of assisted reproductive technologies (ART) in a clinical setting of their choosing. However, the lack of research and awareness regarding the bioethical facet of medical tourism in relation to ART highlights even further the global spectrum of controversy surrounding it.

A computerized search was performed in PubMed employing keywords and combinations including, 'cross-border reproductive care', 'medical tourism', 'legislation of CBRC' and 'social impacts of CBRC'. The total number of published articles provided by our PubMed research was 1905. All articles in English were evaluated based on their title and abstract, without any limitation on their publication date. Emphasis was given to original studies and reviews published by research groups specializing on relevant fields.

2 Drivers behind CBRC

The most common drivers behind CBRC are the cost of treatment, quality of medical care, avoidance of waiting lists, anonymity and accessibility or legal issues regarding the country of origin. These factors determine the countries to which patients choose to travel. At the same time, the very same drivers highlight the social and economic differences between patients, thus creating important ethical issues.

The cost of infertility treatment is one the most popular reasons for patients to seek help outside the borders of their country of origin. Numerous couples prefer destinations where ART is more affordable, irrespective of the success rates reported [7]. Turkey is reported to be an emerging popular destination, since an IVF treatment costs approximately \$8,500, which is considerably lower than in the USA, with an average cost of \$12,400 [8]. Countries such as Norway, Sweden and Spain charge a lower fee, ranging from \$4,500 to \$5,700 [8]. The average cost of treatment per couple reported in other common destinations, such as the United Kingdom (UK), Australia and Germany, ranges over \$4,000 [9,10] if any, insurance, raising critical questions concerning how patients and providers view and make decisions regarding these challenges. In-depth

semi-structured interviews of approximately 1 hour were conducted with 37 IVF providers and 10 patients (17 physicians, 10 other providers and 10 patients). In Pakistan and Iran, the cost of an IVF cycle is approximately \$1,272 [11]. Greece is also a country preferred by overseas patients, because it may be an inexpensive destination, compared to other developed countries [12]

Besides financial reasons, quality of medical care and level of expertise are important factors that patients consider. On that note, Australia and Turkey remain attractive options, as they specialise in ART that provides a high quality of clinical service in IVF treatment [10,13] clinical care, counseling, and support experiences of Australian and New Zealand participants considering or having participated in cross-border reproductive care (CBRC). Also, a considerable number of CBRC patients visit IVF clinics in Japan and India, followed by countries such as America, Italy, Spain, Korea, Germany and China [14]. Cyprus and Greece are also promising destination countries in CBRC, due to the specialized provision of ART techniques and the well-trained accredited scientists [12] The facilities of the clinics should provide the required state-of-the-art equipment, coupled with an excellent standard of patient care. High quality CBRC means that the clinics and the personnel providing services must constantly enrich their knowledge and specialize in new techniques.

Anonymity is another issue concerning all donors, patients, surrogates and other persons involved regarding the social "stigma" that surrounds infertility treatments. Europeans may opt to remain in their home country and receive gametes from anonymous donors through contact with oocyte or sperm donation banks. Countries such as Spain, Denmark or Greece are in favour of anonymity, whereas England forbids it [15]. Most patients prefer to choose an anonymous donor, a fact associated with various ethical concerns. On one hand, everyone should have the right to know their origin. However, it has been voiced that children will grow up in a more protected and healthy family environment if they are not aware of the medical techniques involved in their conception, such as CBRC [16,17] 33 recipients and 12 partners completed an anonymous questionnaire regarding their opinions on the release of identifying information, whether a child should be told about the manner of their conception, the level of expected contact of donor with future donor offspring and the importance of anonymity in their decision to donate. Slightly less than one-half (48.9%). The legislation of most countries claims that gamete or embryo donors have no obligation to financially support the child and that they are excluded from being involved in raising the child, while they have no right to interfere with the manner of

the child's upbringing and the environment in which the child will grow [18]. However, many observers believe that donor anonymity and ignorance on the subject of the child's origin are detrimental to its mental and psychological development. Thus, countries like Ireland have created a network with the personal data of the donors who have contributed to the creation of an offspring, in order to enable these children to research the person that they are genetically linked to [19]. European countries have henceforth been regulated by the General Data Protection Regulation (GDRP/2016/679), which has been in effect since May 25, 2018.

It is understandable that the process of finding the right donor may be particularly time-consuming, resulting in waiting lists [20] candidates were drawn upon as potential matches and presented to the potential recipient, who decided whether to accept the donor. Reasons for accepting or rejecting the donor were tallied and were compared to the patient's wish list. Medical history and race were ranked by 33 and 23% of recipient couples as the two most important characteristics, while 74 and 54% stated that these were among the three most important factors in a potential donor compared with other traits. Fifty-seven (71%). Bypassing waiting lists and an abundance of donors frequently seem to depict the drivers behind CBRC. For that reason, Spain is a popular destination, with short waiting lists and a wide range of possible donors [21]. Patients looking for a destination country with a short waiting list are mainly interested in oocyte and sperm donation, as well as surrogacy. The systems in place and the legislative frame are directly related to delays in receiving treatment, regarding these categories [22].

According to Shenfield et al., it is reported that the main motivating factor for engaging in CBRC is to evade the law, for example, when the specific ART is either forbidden per se or a particular group is excluded from treatment due to social characteristics [23,24].

There are two types of legal prohibitions in CBRC. The first one pertains to who can undergo fertility care, and the second is about constraints that apply to fertility techniques. The restrictions in some countries regarding the patients' age, sexual orientation and marital status constitute drivers towards CBRC [25]. A vast group of patients opting for CBRC refers to homosexual couples, unmarried couples and couples or single persons. For these potentially complex cases, achieving a pregnancy through natural conception is not possible; nonetheless, they have the right to reproductive autonomy that respects their individual rights and protects their diversity [25].

Although the stereotype of the traditional family has been somewhat erased, concerns are still expressed [26]. In

Middle Eastern countries, for example, only opposite-sex married couples have access to reproductive care, with the exception of Israel [27]. Current literature presents clearly that, from a legal standpoint, the care provider is obliged to render services without any discrimination based on the patient's sexual orientation or marital status [9,28] if any, insurance, raising critical questions concerning how patients and providers view and make decisions regarding these challenges. In-depth semi-structured interviews of approximately 1 hour were conducted with 37 IVF providers and 10 patients (17 physicians, 10 other providers and 10 patients). It is apparent that CBRC may help alleviate these difficulties; it should, however, be practiced in a controlled manner [25].

Legislation varies widely between countries and presents differences that could benefit CBRC patients. Japan, similar to China and Saudi Arabia, has banned surrogacy, possibly due to the belief that surrogacy entails an inherent health risk. Thailand outlawed commercial surrogacy for foreigners in 2015 [7]. Oocyte donation is forbidden by law in Germany, and IVF treatment is denied to homosexual couples [3]. In 2004, the Italian government passed a bill stating that only patients with reproductive problems attributed to sterility or infertility are allowed to receive medically assisted reproductive care [29]. On the other hand, countries like Spain and Belgium are a common destination for CBRC, due to their less restrictive legislation [21].

Greece abides by the standards and code of practice suggested by ESHRE and the European Tissue Directive and follows practices similarly adopted by other European countries. Novel protocols employed in IVF practice in Greece, such as the freeze-all strategy, [30] are of equal standard to major European countries such as the UK and Spain. In Greece, according to current legislation, ART is approved for heterosexual couples and single individuals, which is similar to legislation in other European countries, including Spain and Belgium. Moreover, the legislation sets the upper age limit for women to 50 years of age and approves specific ART activities such as surrogacy and gamete donations. In 2013 a study including French patients seeking CBRC reported that most of the patients travelled to Greece regarding oocyte donation. The incentive for patients to choose Greek ART was reported to be the recommendation of a patient organization (77%) and/or the low cost of provided services (91%) [31]. The current Greek legislative framework, along with the high standard of treatment offered in the setting of private fertility centers and the competitive cost of care, appear to have contributed towards the successful growth of the phenomenon of CBRC in Greece.

3 Considerations regarding CBRC and the patients' country of origin

The concerns regarding the country of origin are of ethical, legal and/or financial nature. One of the common economic issues pertains to patients investing their money in a country other than their home. The cost of medical treatment during pregnancy and the cost of birth are major financial burdens for the country of origin in cases where public insurance is in place. The phenomena of ovarian hyperstimulation and multiple pregnancies are the principal, significant complications. Interestingly, almost one quarter of women achieving a pregnancy through fertility treatment abroad is likely to realize a multiple pregnancy [32]. A study reported that for 11 multiple pregnancies achieved by CBRC, the total cost of Australian health care, including both obstetric and neonatal care, exceeded \$1,000,000 [33]. In other instances, patients may face the denial of their insurance coverage both in the country where they received treatment as well as in their home country. Apart from the issue of financial compensation, they also have to deal with the complex possibility of refusal of medical care to address the complication on ethical or legal grounds [4,34].

From a legal aspect, occasionally patients travel to a foreign country to receive treatment because they are driven by access to medical techniques that are illegal in their country, a phenomenon entailing certain risks. In this regard, it has been reported that a country may prosecute its inhabitants who request and consent to treatments that are illegal in their own country [35]. There appears to be a "silent acceptance" from the countries of origin regarding such citizens, irrespective of whether the treatment they have received is illegal in their own country. This situation impugns the importance and the level of application of the national legal decisions of each country [36,37]. Repatriation to the country of origin for offspring born through surrogacy is a distinct issue. Some countries require the adoption of the child by the parents, even if they are genetically related. Therefore, offspring born through surrogacy in a foreign country are stateless until their parents adopt them [36]. Greece may be the only EU Country where no adoption act is required (Article 17 of the Law 4272/2014).

Ethical concerns should be acknowledged in these cases, as patients may fail to be successfully managed and/or compensated when required, with respect to legal or financial matters. The absence of a specified entity such as a board to take responsibility and co-ordinate relevant matters in the Country of origin may contribute to failure

of resolution of series of issues [25,38,39] raising questions about why assisted reproductive technology (ART).

4 Considerations regarding CBRC and the host country

4.1 The financial component

Tourism is a significant source of income for every country. Medical tourism contributes to the country's gross domestic product (GDP) in more than one business area. Beyond the payment for medical treatments, travelers also spend a considerable amount purchasing tickets and planning for accommodation in the destination country. According to a recent study conducted in Turkey, the per capita expenditures of inbound medical tourists are more than double the expenditures of other tourists [3,40].

Nevertheless, health commercialization remains a topic worth investigating in regard to the destination country. Concerns have been raised regarding women from economically weak countries such as India, where their life conditions could render them susceptible to exploitation. Interestingly, in a region of India, surrogacy's "turnover" reached \$445 million [3]. Therefore, the option of being a surrogate mother in some countries reflects a compulsory life choice rather than an altruistic action. Additionally, oocyte donation may present as an option for women to enhance their income [41]. On the other hand, it is believed that donors in these processes should ideally take part voluntarily altruistically in order to avoid any economic exploitation. In an effort to reach moral justice and simplicity in practice, there are studies that report on an ideal scenario based on each country enabling financial compensation for donors [41,42].

Most of a single country's budget originates from the taxes citizens are obliged to pay, but the same budget is employed to target medical treatments and care for foreign patients, thus weakening public health. As a result, a proportion of the general population may be excluded from this type of health care due to its high cost, contributing to social inequality [2,43]. This condition creates a double standard in the case of CBRC. Taxpayers should be the ones who receive the medical benefits and the physician's care, as they are the ones who have invested and paid for such privileges [44].

4.2 The obligation of the assisted conception unit of the host country to ensure optimal practice

The principal consideration during treatment is to ensure safe practice. Patients carrying viral load and infectious agents could pose a threat to personnel, as well as to other patients receiving treatment at the time or to patients that maintain gametes or embryos in storage. It is imperative that assisted conception units (ACUs) treating patients carrying a viral load have the appropriate infrastructure.

Regarding the technique of cryopreservation of oocytes and embryos, special organization and specific programs should be in place. Embryos or gametes should be stored in the CBRC country of destination, but contacting the patients who return to their country of origin may be challenging. Extra diligence should be focused on consent forms and their completion. Reasons for contact may include renewal of consent form, extension of storage or expiry of storage dates as specified by the consent form. For those reasons, it is crucial to ensure efficient communication of the respective ACUs between the country of origin and the country of destination where treatment is received. Cryopreserved material is commonly transported back to the country of origin and possibly included in future treatments. It is, therefore, imperative that both ACUs share information on the patients' management, protocols employed and percentages of success.

With respect to the number of embryos transferred, a very important issue is the legislation of the country of origin of the patients; this should be taken into consideration by the clinics, along with the current country's legislative framework. Clearly, pregnancy complications that present as a result of the embryo transfer procedure will burden the country of origin and its health system. As discussed above, one strategy strongly encouraged for adoption, especially in light of CBRC patients, is elective single-embryo transfer (eSET). Generally, this approach is associated with the best perinatal and neonatal outcomes, minimizing the risks of multiple gestation and preterm birth. However, the clinical data show single implantation outcomes are improved from the transfer of two or more embryos. It is of a great importance to evaluate embryo viability in relation to maternal receptivity in order to achieve a single live birth via eSET. The ACU should rely on a system of a series of key performance indicators (KPI's) that will provide an adequate overview of the most important steps in the IVF laboratory process to establish a universal common practice and efficient internal quality control to enable the ideal practice of eSET [45].

4.3 The need for certification and quality assurance of services provided to the traveller

The majority of patients who are interested in receiving treatment in a foreign country often come from faraway destinations. For the patients to be well informed regarding the management of their cases, success rates, analysis and a reader-friendly version explaining the procedure and the cost of technique should be provided by the clinic. All aspects of the future patient management and care should be carefully considered from a medical, financial and psychological point of view, as complications may refer to obstetric, perinatal and pediatric issues. It is important to provide appropriate infrastructure and treatments for complex patient cases and handle them with respect and discretion. CBRC centers should be audited, approved and certified by reliable providers of quality in International Medical Care.

Audits should ensure optimal practice and trustworthiness of the CBRC center and take into consideration the legal and ethical barriers that exist by prioritizing safe and effective care and management of the patients. Vital information on the hygiene, techniques, clinician expertise, cost of the treatments and, finally, legal and ethical issues that may arise should be readily accessible. The ACU must be transparent and fully disclose pricing for all services to help avoid reported cases of patient-generated debt following treatment [7]. Another important issue that clinics should address is the language barrier, which can result in confusion and partial disclosure of technical information on treatment and potential perils. It is not unusual for patients to not fully understand what the treatment entails, which may lead to a management challenge in claims for compensation [46]. In some cases, patients interested in receiving treatment through medical tourism may not even be fully informed on the techniques and the risks they may involve. Clinics may promote and advertise the novelty of a new technique to strongly appeal to prospective patients, while failing to provide full disclosure about unknown factors and related implications [45,47]. An approach towards a more universal protocol has been attempted in Europe through the efforts of the European Board and College of Obstetrics and Gynaecology (EBCOG). The EBCOG has proposed several standards of care that have resulted in a more consistent clinical practice among the European Countries [48] which require clarification. Over the past 20 years, reliable methodology has been developed for the management of infertile couples. This includes high quality diagnostic and therapeutic procedures, which are applied in highly special-

ised infertility centres. The European Board and College of Obstetrics and Gynaecology (EBCOG).

Clinics should properly train their staff to deal with any incident to secure the patient's safety and reduce the possibility of poor management. Furthermore, it is of vital importance that clinics include a coordinating team that will collect the medical history of each patient and advise the travellers on matters of interest. The need for certification and quality assurance of services is imperative.

5 Conclusion

CBRC is a multifactorial and multifaceted phenomenon that requires travellers to make decisions on various challenging issues [49]. Although the search for treatment in foreign countries is common in ART, there are multiple issues and challenges that need to be delineated and standardized to ensure optimal practice in CBRC. Issues such as repatriation of offspring, decisions regarding surrogacy, management of complications during and after treatment, high-risk pregnancies, multiple pregnancies as a result of treatment and legal and bioethical standpoints are the core of this trend. The purpose of this study is to analyse the drivers and risks behind CBRC and to focus on challenging issues regarding optimal practice and how to ensure it. Most importantly, controversies, discrepancies and unresolved issues surrounding the subject of CBRC became clear during our literature search. This study calls for research into the motivation of CBRC travellers and an efficient analysis of the process of travelling for fertility treatment. The need for data on such issues in medical tourism has been aptly highlighted by other studies on cosmetic surgery tourists [50]. The timely nature of this analysis is underscored in the current review, strengthening the need to suggest and implement an international governance system [51], to address the challenges that CBRC presents. Promotion of universal access and monitoring of CBRC cycles is imperative for ensuring safety and effectiveness for the travellers seeking fertility treatment in a foreign country.

Authors Contribution

Mara Simopoulou: conception of the study, literature search, study design, analysis, and manuscript drafting. Konstantinos Sfakianoudis: literature search, study design, analysis, and manuscript drafting. Polina Giannelou: literature search, manuscript drafting. Aikaterini

Pierouli: literature search, manuscript drafting. Anna Rapani literature search, manuscript drafting. Evangelos Maziotis: literature search, manuscript drafting. Dionysios Galatis: literature search, manuscript drafting. Panagiotis Bakas: analysis, manuscript editing. Nikos Vlahos: analysis, manuscript editing. Konstantinos Pantos: manuscript editing, critical review. Michael Koutsilieris: manuscript editing, critical review.

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