

Comparative bibliometric analysis of fertility preservation

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Abstract

Aim: Fertility preservation (FP) has become an important issue for both women and men, due to oncological therapies, gonadotoxic treatments, surgeries, and infertility. The aim of this study is to investigate the publications related to FP, identify the top effective countries and journals, top productive researchers, and trend topics.

Material and Methods: The data of this study were obtained using the Thomson Reuters WoS (Thomson Reuters, New York, NY, USA) database, separately for females and males. In the bibliometric analysis, 'fertility preservation' was used as a keyword. VOSviewer (Version 1.6.6) was utilized for bibliometric network visualizations. SPSS was used for the statistical analyses (Version 22.0)

Results: Analysis results of the keywords used for men indicated 817 publications and for females indicated 2531 publications totally. The United States of America (USA) was the top country for the publications about both genders. The top three research fields for both genders were Obstetrics and Gynecology, Reproductive Biology, and Oncology. The journals that contributed to the literature most were Fertility and Sterility and Human Reproduction respectively in both gender categories. The correlation between the number of total fertility preservation articles and total cancers, Gross Domestic Product-World Bank (GDP-WB), Gross Domestic Product-International Monetary Fund (GDP-IMF), Human Development Index (HDI), and Internet Users (IU) was significant ($r=0.482$, $p=0.017$; $r=0.609$, $p<0.001$; $r=0.620$, $p<0.001$; $r=0.365$, $p=0.043$; $r=0.479$, $p=0.006$).

Conclusion: It has been determined that researches on the protection of the fertility of cancer patients and infertile patients have increased from past to present. Also, it is observed that the economies of countries have an active role in research productivity.

Keywords: Bibliometrics; fertility preservation; female; male.

INTRODUCTION

Fertility capacity in both females and males might decrease due to such factors as advanced age, genetic syndromes, gonadotoxic treatments, and various malignancies. Fertility Preservation (FP) has become an important issue for both women and men at reproductive age as well as girls and boys at pre-pubertal period. Majority of previous research and reviews were about FP in cancer patients (1,2). However, sometimes FP is needed in clinical cases excluding cancer (advanced age, endometriosis, autoimmune diseases, genetic syndromes damaging male spermatogenesis, etc.), in gonadotoxic treatments, and even for non-medical reasons. All individuals who want to preserve their fertility capacity should be provided with consultancy about the FP methods and their success.

FP is important in males because spermatogonium is easily affected by chemotherapy and radiotherapy. Cryopreservation is the only method that is proven

to preserve male fertility; the success of hormone treatments has not been observed (3). Testicular tissue cryopreservation for male FP could be recommended for boys at pre-pubertal period, but its reliability is still debated (4). There are more FP methods for women in comparison to men. The most common options are oocyte and embryo cryopreservation methods. Oocyte cryopreservation has become a more preferred method by girls at pre-pubertal period and by single women (5). Metaphase II embryo cryopreservation could be considered as the first option in women at post-pubertal period or in married couples (1). Pregnancy happens after the autotransplantation of the entire or some part of ovarian tissue, and it can be used as a FP method (6,7).

Bibliometrics is a comprehensive discipline that enables to analyze the academic literature and to define publications in a specific field (8,9). Bibliometric reports enable to view productivity of the authors and countries about a specific topic, publication trends according to topics and

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years, country and language distributions of the published articles, co-authoring trends, and the preferences of the publishing journals (10,11). Parallel to the increased number of publications in literature, there has been an increase in the number of studies showing important publications through bibliometric analyses, an important method that summarizes publications on a specific topic like meta-analysis results (12,13).

The purpose of this study is to investigate the publications about FP. It also aimed to find out the correlation between the financial and technological opportunities of countries and their productivity in FP studies. With the data obtained from the present study, we aimed to identify the top effective countries and journals, top productive researchers, and trend topics.

MATERIAL and METHODS

The data of this study were obtained by using the Thomson Reuters WoS (Thomson Reuters, New York, NY, USA) database. As patient management varies across genders, we detailed our Search in WoS database under male and female sub-titles. Search for males was done by excluding "postpartum", "female", "females", "women", "oocyte", "ovary", "ovarian" and "hysterectomy" keywords from the "fertility preservation" keyword (Topic: ("Fertility Preservation") Not Topic: ("Postpartum") Not Topic: ("Female") Not Topic: ("Females") Not Topic: ("Women") Not Topic: ("Oocyte") Not Topic: ("Ovary") Not Topic: ("Ovarian") Not Topic: ("Hysterectomy"), Document Types: (Article or Proceedings Paper), Timespan: 1975-2017). Search for females was performed by excluding "Male", "Sperm", "Testis", "Seminiferous", "Spermatogenesis", "Semen", "Testicular", "Spermatogonial" and "Azoospermic" keywords from the "fertility preservation" keyword (Topic: ("Fertility Preservation") Not Topic: ("Male") Not Topic: ("Sperm") Not Topic: ("Testis") Not Topic: ("Seminiferous") Not Topic: ("Spermatogenesis") Not Topic: ("Semen") Not Topic: ("Testicular") Not Topic: ("Spermatogonial") Not Topic: ("Azoospermic"), DocumentTypes: (Article or Proceedings Paper), Timespan: 1975-2017). The study included the documents published between 1975 and 2017 and excluded the ones published in 2018. Publications produced from England, Scotland, Wales, and Northern Ireland were collected in the United Kingdom (England) title.

VOSviewer (Version 1.6.6) was utilized for bibliometric network visualizations (14). SPSS was used for the statistical analyses (Version 22.0, SPSS Inc., Chicago, IL, USA; licensed to Hitit University, Corum, Turkey). While the normally distributed statistics were demonstrated as mean±standard deviation, categorical variables were shown as the number of cases and percentages. Shapiro-Wilk normality tests were utilized for the evaluation of the distributions of the groups. For the second hypothesis of the present study that investigated a possible correlation between the number of publications and the productivity and developmental features of the countries, the correlation between two continuous variables was analyzed using Spearman's correlation test. Statistical significance was

taken $p < 0.05$.

RESULTS

Total Number of Publications

Analysis results of the keywords used for men indicated 817 publications. Of all these publications, 393 (48.1%) were Articles, 255 (31.2%) were Meeting Abstracts, 71 (8.7%) were Reviews, 62 (7.6%) were Editorial Materials, 25 (3.1%) were Letters, 13 (1.6%) were Proceeding Papers, and 11 (1.3%) were other publications (Correction, Book chapter, News item). Analyses results of the keywords for females indicated 2531 publications totally. Of all these publications, 1486 (58.7%) were Articles, 442 (17.5%) were Meeting Abstracts, 369 (14.6%) were Reviews, 158 (6.2%) were Editorial Materials, 69 (2.7%) were Proceeding Papers, 48 (1.9%) were Letters, and 24 (0.9%) were other publications (Correction, Book chapter, News item).

Bibliometric analyses for men were performed with 397 out of 817 publications that were articles and proceeding papers. h-index for these 397 publications was 42, average citations per item were 15.91 and sum of times cited was 6315. Bibliometric analyses for women were performed with 1503 out of 2531 publications that were articles and proceeding papers. H-index for these 1503 publications was 79, average citations per item were 19.97 and the sum of times cited was 30010.

Development of the Publications

The first study about women and men was published in 1983. While the publications about female FP began to increase rapidly in 2007, publications about male FP began to accelerate in 2011 (Figure 1). A number of publications and citations was higher for women. Distribution of the number of publications according to years was given in Figure 1, and the distribution of the number of citations was given in Figure 2. The United States of America (USA) was the top country for the publications about both genders, and the rank order of the other 10 countries was given in Figure 3.

Research Fields

The top three research fields for both genders were Obstetrics and Gynecology, Reproductive Biology, and Oncology respectively. The top 10 fields investigated for men and women are shown in Table 1.

International Collaboration

There were 37 countries out of 67 that had at least 5 publications about female fertility. Collaboration between these countries is given in Figure 4a. There were 20 out of 50 countries that had at least five publications about male fertility. Collaboration between these countries is given in Figure 4b.

Co-citation

Co-citation analyses showed that there were 18217 authors who searched female FP. Figure 5a displays the bibliometric network of 119 authors who received at least 50 citations. Figure 5b displays the bibliometric network of 80 out of 7715 authors who had at least 20 co-citations about male FP.

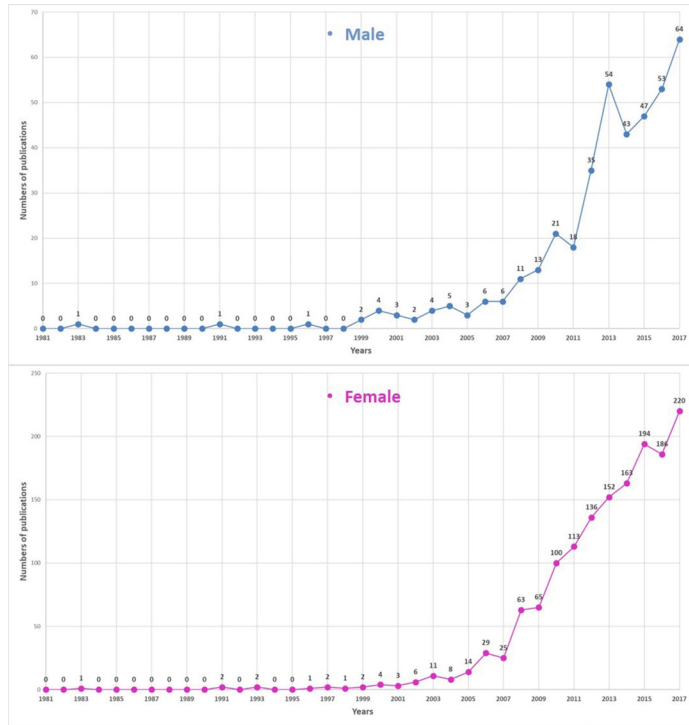


Figure 1. Change of publication numbers by years in both genders

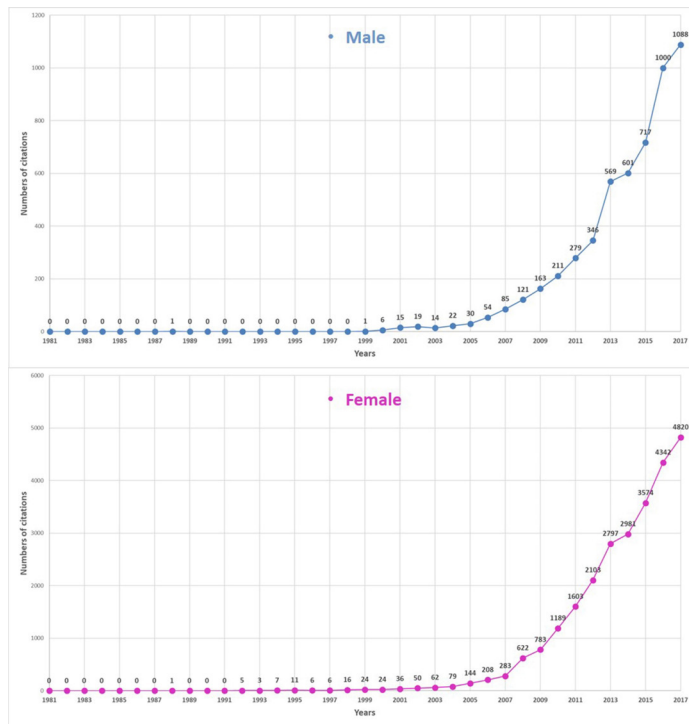


Figure 2. Change of citation numbers by years in both genders

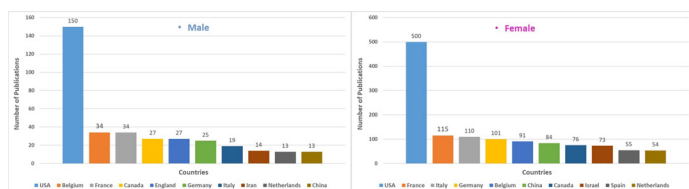


Figure 3. The most productive 10 countries in both genders

Table 1. The first 10 research areas on fertility preservation for male and female

Research Areas	Male		Female	
	C	% of 397	C	% of 1503
Obstetrics	134	33.8	838	55.8
Gynecology				
Reproductive Biology	121	30.5	560	37.3
Oncology	89	22.4	340	22.6
Endocrinology	40	10.1	94	6.3
Metabolism			Genetics Heredity	
Urology Nephrology	31	7.8	76	5.1
			Endocrinology	
			Metabolism	
			General Internal	
			Medicine	
			Science Technology	
			Other Topics	
			Hematology	
			Developmental	
			Biology	
			Surgery	

C: Count

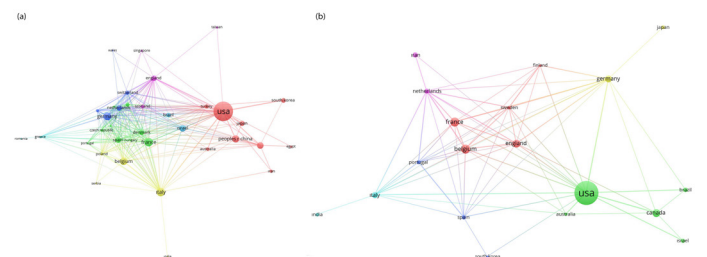


Figure 4. Network visualization map of international collaboration analysis; (a) for female (b) for male



Figure 5. Network visualization map of co-citation analysis of active authors (a) for female (b) for male

Top Published and Cited Journals

The journals that contributed to the literature most were Fertility and Sterility and Human Reproduction respectively in both gender categories. Table 2 presents the top 15 journals about men and women that contributed to the literature most. Table 2 also demonstrates the number of citations in the journals.

Figure 6a displays the density map of 61 out of 401 journals about female FP that had at least 5 citations. Figure 6b demonstrates the density map of 60 out of 200 journals about men that had at least 2 citations.

Active Authors

While Rives N was the top-cited author about male FP, Wynn C was the top-cited author about female FP. While Andersen CY was the top author and the top cited author about FP, this was followed by Oktay K. Table 3 displays the top 10 authors that contributed to the literature most for men and women.

Table 2. The first 15 journal source by number of publications and citationson fertility preservation for male and female

Male			Female		
Journal Name	No	% C	Journal Name	No	% C
Fertility and Sterility	39	9.8 566	Fertility and Sterility	139	9.2 5114
Human Reproduction	32	8.1 1420	Human Reproduction	124	8.3 5216
Pediatric Blood Cancer	10	2.5 319	Journal of Assisted Reproduction and Genetics	83	5.5 1125
Journal of Adolescent and Young Adult Oncology	8	2 71	Reproductive Biomedicine Online	48	3.2 1069
Journal of Assisted Reproduction and Genetics	8	2 65	Gynecologic Oncology	31	2.1 892
Andrologia	7	1.8 75	International Journal of Gynecological Cancer	31	2.1 418
Journal of Urology	7	1.8 173	Gynecological Endocrinology	22	1.5 182
Plos ONE	7	1.8 63	Plos ONE	21	1.4 188
Andrology	6	1.5 75	European Journal of Obstetrics Gynecology and Reproductive Biology	19	1.3 147
Asian Journal of Andrology	5	1.3 31	GynecologieObstetriqueFertilité	17	1.1 56
Human Fertility	5	1.3 41	Journal of Adolescent and Young Adult Oncology	17	1.1 94
ActaHaematologica	4	1 19	Seminars in Reproductive Medicine	17	1.1 292
European Journal of Obstetrics Gynecology and Reproductive Biology	4	1 141	Archives of Gynecology and Obstetrics	16	1 297
Reproduction Fertility and Development	4	1 73	Cancer	15	1 943
Urology	4	1 71	Journal of Ovarian Research	15	1 81

No: Number of publications; C: Citations

Table 3. The first 10 authors by record count and citation on fertility preservation for male and female

Male				Female			
Authors	Record Count	% of 397	Citation	Authors	Record Count	% of 1503	Citation
Rives N	17	4.28	334	Andersen CY	42	2.79	2349
Goossens E	15	3.78	264	Oktay K	40	2.66	2316
Tournaye H	14	3.53	299	Donmez J	31	2.06	1518
Wyns C	11	2.77	541	Woodruff TK	31	2.06	1026
Quinn GP	10	2.52	229	Dolmans MM	30	2.00	1471
Schlatt S	10	2.52	384	Dittrich R	23	1.53	528
Bironneau A	9	2.27	116	Meirow D	22	1.46	838
Milazzo JP	9	2.27	173	Beckmann MW	20	1.33	338
Mace B	8	2.02	189	Shea LD	20	1.33	798
Ehmcke J	7	1.76	343	Ernst E	19	1.26	1394

Table 4. The 10 most cited manuscripts on fertility preservationfor male

No	Article	Author	Journal Name/Published	TC	AC
	Methods of cryopreservation of testicular tissue with vitablespermatogonia in pre-pubertal boys undergoing gonadotoxic cancer treatment.	Keros, Vivia; Hulthenby, Kjell; Brogstorm, Birgit; et al	Human Reproduction-2007	142	11.83
	Cryopreservation and thawing is associated with varying extent of activation of apoptotic machinery in subsets of ejaculated human spermatozal.	Paasch, U; Sharma; RK; Gupta, AK, et al	Biology of Reproduction-2004	141	9.40
	Spermatogonial stem cell transplation into rhesus testes regenerates spermatogenesis producing functional sperm.	Hermann, Brian p; Sukhwani, Meena; Winder, Felicity; et al	Cell Stem Cell-2012	122	17.43
4	Options for fertility preservation in prepubertal boys.	Wyns, Christine; Cruaba, Mara; Vanabelle, Bernard ; et al	Human Reproduction Upoate-2010	122	13.56
5	Characterization , cryopreservation , and ablation of spermatogonial stem cells in adlutrhesus macaques	Hermann, Brian p; Sukhwani, Meena; Lin, Chih-Cheng; et al	Stem Cells-2007	120	10.00
6	Positive and negative psychasacialimpac of being diagnosed whit cancer as an adolescent or young adult	Beillzrn Keith M: Smith, Ashley Schmltd. Steven et al.	Cancer-2012	117	16.71
7	Long-term spermatogonialsurvial in cryopreserved and xenografted immature human testicular tissue	wyns, christine, Van Langendonckt, Anne, wese, francos, Xaver, et al	Human Reproduction-2008	94	8.55
8	Adolescent and young adlut oncology	Coccia, Peter F, Altman, Jessica, phata, Smita, et al.	Journal of The National Comprehensive Cancer Network-2012	92	13.14
9	An experimental pretocal for fertility preservation in prepubertal boys recently diagnosed whit cancer: A report of acceptability and safety.	Ginsberg, JP;Carson, C.A; Lin, K; et al.	Human Reproduction-2010	89	9.89
10	Effect of cold storage and cryopreservstion of immature non-human premate testicular tissue on spermatigonial stem cell potential in xenografts	Jahnukainen, Kirst: Ehmke. Jens; Hergenröther. Scott D et al.	Human Reproduction-2007	88	7.33

TC: Total Citation; AC: Average Citations per Year

Significant Publications

The top-cited article about male FP was the study conducted by Keros V. et al. who investigated testicular tissue cryopreservation in 2007. The top-cited article in

female FP was the study conducted by Andersen C. et al., who investigated ovarian tissue transplantation in 2018. The top-cited 10 publications for men are given in Table 4, and those for women are given in Table 5.

Table 5. The 10 most cited manuscripts on fertility preservation for female

No	Article	Author	Journal Name/Published	TC	AC
1	Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue	Andersen, Claus Yding; Rosendahl Mikkel; Ryskow, Anne Grete et al.	Human Reproduction-2008	287	25.09
2	Fertility preservation in breast cancer patients: A prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation	Oktay K; Buyuk, E Libertela, N et al.	Journal of Clinical Oncology-2005	276	19.86
3	Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation	Donnez, Jacques, Dolmans, Mane Madeleine Pellices, Antonto; et al.	Fertility and Sterility-2013	250	41.67
4	Fertility preservation: Successful transplantation of cryopreserved ovarian tissue in a young patient previously treated for Hodgkin's disease	Dermeestere, tsabelle, Simon, phippe,Emibant, Serena, et al.	Oncologist-2007	245	20.42
5	Safety of fertility preservation by ovarian stimulation with letrozole and Gonadotropins in patients with breast cancer: A prospective controlled study	Azim, Am A:Costantini-Ferrando, Marla, cktay, Kutluk	American Journal of Obstetrics and Gynecology-2008	240	21.82
6	Uterine artery embolization: An underused method of controlling pelvic hemorrhage	Vedantham, & Goodwin, SC Mctucas, B, et al.	American Journal of Obstetrics and Gynecology-1997	234	10.64
7	Acute ovarian failure in the childhood cancer survivor study	Chemaltily,W: Mertens,AC; Mitby,bP et al.	Journal of Clinical Endocrinology & Metabolism-2006	221	17.00
8	The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer	Anderson,RA.Themmen APN; Al-Qahtani, A:etal	Human Reproduction-2006	219	16.85
9	Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy	Oktay, KutlukHourvitz, Artel; Sahin, Gulnazetal	Journal of Clinical Endocrinology & Metabolism-2006	212	16.21
10	Primary ovarian insufficiency	De Vos, Michel; Devroey, Paul; Fauser, Bart C.J. M	Lancet-2010	204	22.67

TC: Total Citation; AC: Average Citations per Year

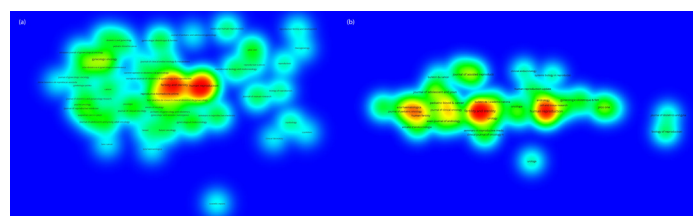


Figure 6. Density visualization map of citation analysis of active journals (a) for female (b) for male

Trend Topics

Of the 1503 publications about female FP, 2245 keywords were used, and these keywords included 72 keywords that were used at least 10 times in different publications. These most frequently used keywords included “fertility preservation, cancer, fertility, breast cancer, and chemotherapy”. Figure 7a displays the map of the most frequently used words and the relationship between the words. As for men, 750 keywords were used in 397 publications, and these publications included 44 keywords

that were used at least five times in different publications. The most frequently used keywords were “fertility preservation, cancer, cryopreservation, chemotherapy, and Klinefelter syndrome”. Figure 7b displays the map of the most frequently used words and the relationship between the words.

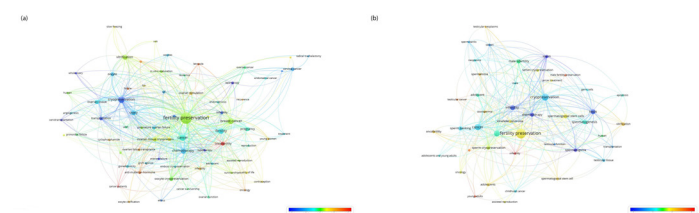


Figure 7. Network visualization map of relationships between the most commonly used trend keywords (a) for female (b) for male

The Relationship between Fertility Preservation and World Cancer and Development Level
This study investigated the relationship between world

cancer data, internet users and human development index. Correlation between the number of articles on female fertility and gynecologic cancers, Gross Domestic Product World Bank (GDP-WB), Gross Domestic Product International Monetary Fund (GDP-IMF), Human Development Index (HDI), Internet Users (IU) was significant ($r=0.538$, $p=0.007$; $r=0.603$, <0.001 ; $r=0.591$, <0.001 ; $r=0.357$, 0.049 ; $r=0.456$, 0.010). Correlation between the number of articles on fertility preservation and male cancers, GDP-WB, GDP-IMF, IU was significant ($r=0.383$, $p=0.044$; $r=0.571$, 0.001 ; $r=0.603$, <0.001 ; $r=0.470$, 0.008). No relationship was found between male fertility preservation and HDI ($p=0.211$). The correlation between the number of total fertility preservation articles and total cancers GDP-WB, GDP-IMF, HDI, IU was significant ($r=0.482$, $p=0.017$; $r=0.609$, <0.001 ; $r=0.620$, <0.001 ; $r=0.365$, 0.043 ; $r=0.479$, 0.006).

DISCUSSION

Chemotherapeutics used in cancer treatment were first identified after World War II. The first chemotherapeutic identified, nitrogen mustard, was used in the treatment of lymphoma (15). Hundreds of chemotherapeutic agents and treatment protocols have been developed until today. The patients' life expectancy has increased thanks to the biotechnologies and pharmacological agents developed. As patients have healthy life changes in their remaining life, there is a need for fertility preservation, and the studies have progressed in this direction. This study aims to present the studies on fertility preservation and the momentum gained so far in from a wide perspective.

New and sensitive treatment alternatives have been developed in order to protect fertility after genotoxic treatments. Basic fertility preservation methods could be summarized as oocyte freezing for women and freezing the sperms obtained from ejaculation or testis for men. Embryo freezing could also be an option for married people or couples who have an expectation of a child. Preservation of the entire gonad or some part of gonad tissue for protecting fertility has also yielded successful results (16). Although the fertility preservation techniques were developed due to oncological treatments, they are successfully used in order to be protected from the causes of infertility such as genetic disorders and ovarian failure (17,18).

The USA is the most experienced country in diversifying, planning and applying the fertility-preserving treatments. In a similar vein, researchers and researches that took an active role in fertility-preserving treatments have been in the USA, which was followed by the high productivity of the European countries. France, Germany, Italy, and Belgium had high productivity among the European countries; developing countries had notable developments in Asian countries; the People's Republic of China had notable efforts, and Japan, Israel, and Turkey were found to be more productive. There was a significant correlation between Fertility Preservation publication productivity in

male, female, and common category and GDP, HDI and IU as indicators of development the countries, which demonstrates a direct connection with the contribution to the related literature.

When the fertility-preserving treatments are investigated separately in terms of genders, tissue and sperm freezing methods and stem cell treatments were identified for protecting male fertility, and they became pioneer studies in their field. For instance, the study conducted by Keros et al. reported less tissue damage as a result of the preservation of the testis tissues collected in puberty period with new methods for protecting male fertility; our bibliometric analyses results found this study as the top-cited publication for fertility preservation (19). Animal studies have shown that stem cell therapy applied for male fertility is beneficial and that it is possible to obtain live spermatogonium (20).

One of the most important steps taken for preserving female fertility was the autotransplantation of the frozen ovarian tissue and the pregnancies obtained identified by Andersen et al. Bibliometric analysis results of the present study showed that this study was the top-cited publication in female fertility preservation. In addition, the second top-cited publication written by Oktay et al. reported that ovulation induction done with tamoxifen in patients with breast cancer which is followed by embryo cryopreservation is one of the important steps of preserving female cancer patients' fertility (21). The study that received the highest number of annual citations was the review article written by Donnez et al., which investigated 60 ovarian cryopreservation (7).

Publications about preserving male fertility started in 2010 with publications about cryopreservation techniques and with patients receiving chemotherapy; the issue of fertility preservation was investigated from the infertility aspect and in terms of azoospermic patients in 2015 and later. Publications about female fertility preservation were similarly written about cryopreservation methods and ovarian tissue transplantations, and the publications in 2015 and later have usually been about oncofertility and the agents used in oncofertility. Fertility and Sterility and Human Reproduction were the journals that had the highest contribution to the literature.

Co-citation analysis in the issue of male fertility was grouped around two authors. While the studies of the first author, Leslie R. Schover, and her team focused on oncofertility, studies by Christine Wyns and her team focused on fertility preservation of boys at pre-pubertal period. Publications about female fertility preservation were centered around KutlukOktay and Jacques Donnez. Both authors had publications about oncofertility.

The present study found that the gynecologists worked together with pediatricians, endocrinologists, and oncologists. Fast access to interdisciplinary health team would make it easier for patients to maintain their fertility.

The present study is the only bibliometric analysis

study in the literature that evaluates fertility-preserving treatments. Previous studies involve bibliometric studies that evaluated infertility treatments. A bibliometric analysis that assessed male infertility showed that the most productive country was the USA (22).

This study has a number of limitations. One of them is that we could not give the post-treatment success rates of the countries that applied fertility-preserving treatments, and classification of the fertility-preserving treatments might have been prevented by the fact that the data did not include the pediatric age group. The second limitation of the study might be the data loss caused by the WOS database we used. WOS database might not have listed a number of publications listed in other databases, which might have decreased the number of studies included in the study. However, the WOS database indexes the journals with a higher impact factor in comparison to PubMed, Scopus, Google Scholar indexes, which increases the reliability of our study.

CONCLUSION

There seems to be an increase in the number of publications on fertility preservation as well as the fertility chances of cancer patients. Studies increase under the guidance of teams in the USA, and some authors enable to make progress in this issue. It was found that the studies that investigated women's fertility preservation were higher in number, and these studies started earlier. We also found that male fertility preservation studies included the pediatric age group and the active participation of pediatricians. We observed that all publications on fertility preservations were produced in the oncology area, and immune and genetic causes of infertility were also investigated recently. The issue of fertility was found to be valued by two journals, and totally the most productive authors were found to publish in these journals. The most prominent journals for female and male fertility preservation were found to be Fertility and Sterility and Human Reproduction. Higher relationship of publication productivity with GDP in comparison to HDI shows that financial power directly affected the leadership of a country regarding fertility.

Competing interests: The authors declare that they have no competing interest.

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