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A Holistic View of In Vitro Fertilization Studies: A Bibliometric Analysis

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Abstract

Invitro fertilization is used to aid fertility or prevent genetic problems and assist in having children. IVF is the most effective form of assisted reproductive technology. Bibliometrics is the analysis of the works produced by the determined people/institutions.

The data analyzed in the study were downloaded from the Web of Science (WoS) Core Collection database. Considering these criteria, 13269 articles were found as a result of the search. The data of these articles were downloaded in “plain text” format and uploaded to the SciMAT program and analyzed.

The distribution of the reviewed articles has been determined that very few publications were made before 1990, a significant increase was recorded in the publications in 1991. It is seen that the USA stands out with 3716 articles and ranks first. It is seen that the first two most cited articles were published by The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. According to findings, the terms “in vitro fertilization” (n=10637), “pregnancy” (n=2471), and “women” (n=1928) were found to be the most used keywords.

This study analyzed the studies on Invitro fertilization in the literature by the bibliometric method. It is considered that the data obtained from the article will be useful to researchers working on the subject.

Keywords: Invitro fertilization, Bibliometrics, Science Mapping, Web of Science.

Introduction

Invitro fertilization (IVF) is a complex set of procedures used to aid fertility or prevent genetic problems and assist in having children. During IVF, mature eggs are collected from the ovaries and fertilized by sperm in a laboratory. Then the fertilized egg (embryo) or eggs are transferred to the uterus. IVF is the most effective form of assisted reproductive technology. The procedure may be done using a couple's eggs and sperm or may involve eggs, sperm, or embryos from a known or anonymous donor. The chances of having a healthy baby through IVF depend on many factors. IVF can be time-consuming, expensive, and invasive, resulting in multiple pregnancies. The first birth with the IVF method took place in 1978. Today, millions of births are taking place with the IVF method worldwide. 1-3 % of annual deliveries worldwide are performed by the IVF method. Increasing demand for fertility treatment is driving the development of research and technologies to optimize IVF regimens and success **[1]**.

Bibliometrics is the analysis of the works produced by the determined people/institutions in the determined area, in the determined time, and the relations between these works. Scientific publications are increasing in quantity. With this increase, it has become difficult to follow and analyze scientific developments. Changes in different disciplines or their dynamics should be monitored by scientists. Those working in the academic field demand to stay up-to-date and access the data they need at any time. These demands and needs have triggered the use of bibliometric methods **[2,3]**.

Bibliometrics is based on performing various analyzes on data obtained from databases. As a result of these analyzes, a panoramic view of the subject or discipline can be obtained. In this way, information can be obtained about scientists, works, and articles related to the subject or discipline, and information about their publication performances can be reached. The bibliometric analysis allows us to examine the literature extensively and to see the subject at one point. In addition, it gives information about the citation performances of the works. This information obtained is important in the evaluation of the scientific competence of the works. The aging rate of the literature can be calculated by citation analysis studies performed with bibliometric methods, and accordingly, the attitudes of libraries towards the relevant literature are decided **[4,5]**.

One of the main uses of bibliometrics is scientific mapping. Scientific mapping is the analysis of relationships between different elements that make up scientific disciplines, such as universities, various works, and authors. Science Mapping can also be defined as the visualization of a science discipline **[6]**.

There is much software used for scientific mapping. Gephi, UCINET, Pajek, CopalRed, Cytoscape, CiteSpace II, VOSviewer are some of the software in question.

The aim of this study is to analyze the studies on Invitro fertilization in the literature by the bibliometric method.

Materials and Methods

The data analyzed in the study were downloaded from the Web of Science (WoS) Core Collection database. The search criteria used in the database regarding the subject are presented below. [**"in vitro fertilization"** (Topic) or **"tube baby"** (Topic) and **2021** (Exclude–Publication Years) and **Articles** (Document Types) and **Obstetrics-Gynecology** (Web of Science Categories) and **Science Citation Index Expanded (SCI-EXPANDED)** or **Social Sciences Citation Index (SSCI)** (Web of Science Index) and **English** (Languages)].

Considering these criteria, 13269 articles were found as a result of the search (https://apps.webofknowledge.com). The data of these articles were downloaded in “plain text” format and uploaded to the SciMAT program and analyzed. Before the analysis, seven articles related to the years 1965-1981 were excluded from the analysis because they did not contain the data necessary for the analysis. The keywords used in the articles are grouped by considering their features such as singular/plural, synonymy, and abbreviation. The data were divided into the periods 1990-1999, 2000-2009, and 2010-2020 for analysis. There were 3044 articles in the first period, 4194 articles in the second period, and 6024 articles in the last period.

The SciMAT program configurations used in the analyzes are presented below:

- Unit of analysis: Words (author Role=true, source Role=true, added Role=true).
- Kind of network: Co-occurrence,
- Normalization measure: Equivalence index,
- Cluster algorithm: Simple Centers,
- Evolution measure: Inclusion index,
- Overlapping measure: Inclusion index.

In the analysis findings, it was seen that the theme of "In vitro fertilization" emerged as a dominant motor theme in all three periods, and the word group "In vitro fertilization" was excluded from the analysis to examine other important themes related to the subject.

The findings obtained as a result of the analyzes made by considering these criteria are presented with strategic diagrams, overlap maps, and thematic development map visuals. The sizes of the themes in the strategic diagrams and thematic development map vary depending on the number of publications. The quality evaluations of the themes were made by considering the number of publications, the total number of citations, and the h-index values.

In strategic diagrams, themes take place according to centrality and intensity levels. Themes with strong external correlations, that is, high centrality, are seen on the right side of the diagram, while themes with strong internal correlations, that is, high density, are seen on the upper side.

- Motor themes with high centrality and intensity are located in the upper right area (Motor Themes). These themes express high density and high centrality and are developed and necessary motor themes. They are important for structuring a workspace. Keywords in the motor theme have strong internal links. This makes them more "advanced" as they commonly appear together. They are important for shaping the study topic and include well-developed themes.
- Developed and isolated themes with low centrality and high density are placed in the upper left area (Highly Developed and Isolated Theme). This theme expresses higher density and lower centrality. It is highly developed but isolated. Advanced and isolated themes are themes that are not developed enough. But it is important for the development of the study topic.
- Emerging or disappearing themes with low centrality and intensity are located in the lower-left area (Emerging or Declining Themes). These themes are emerging or declining themes. It includes themes with low centrality and low-density values. They are new themes that may emerge or go beyond the research field to become better. These themes are not only poorly developed but also of low importance to the subject of study.
- Basic and transformational themes with high centrality and low intensity are located in the lower right area (Basic and Transversal Themes). They are low density, high centrality themes. A lot of research has been done on these core themes and they have well-developed interconnections. It is of vital importance to the subject of study. It is seen that the most repeated and most related words are included in this theme. Themes with a large number of articles are mainly located in this area, which is quite logical. Because the main and variable themes are the main focus of the study.

In the overlap map, the numerical development of the keywords used in the articles was visualized by considering the analysis periods. In the thematic development map, the relationships of the themes between the periods are given and the thickness of the lines is shaped in parallel with the strength of the relationship. Solid lines indicate that the same keywords are shared between the themes as the theme names, and dashed lines indicate that common words are shared except for the theme names.

Results

The distribution of the reviewed articles on IVF over the years is given in **Figure 1**. As seen in the graph, it has been determined that very few publications were made before 1990, a significant increase was recorded in the publications in 1991, and the number of publications tended to increase gradually, although there were partial decreases in the number of publications from time to time.

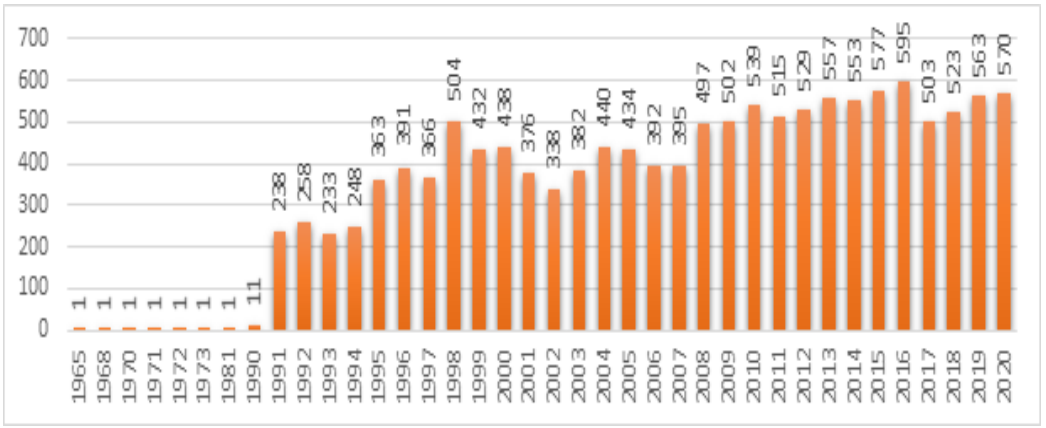

Figure 1: Number of Publications by Years

The distribution of articles published on IVF by country is given in **Figure 2**. When the graph is examined, it is seen that the USA stands out with 3716 articles and ranks first. According to the number of articles, the USA is followed by the UK with 1044 articles and China with 861 articles. Turkey is in 10th place with 549 articles.

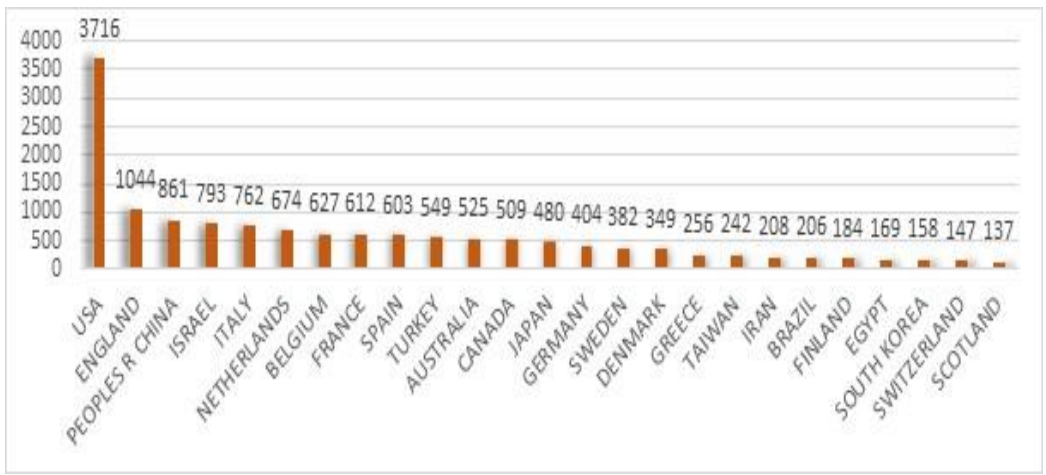

Figure 2: Number of Publications by Country

Information on the five most cited articles is given in **Table 1**. According to this information, it is seen that the first two most cited articles were published by "The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group". The article published by Van Steirteghem et al follows these articles. Considering the period of publication of the article published by Ferraretti et al. in 2011, which ranked fourth, the high number of citations (n=1036) was considered as an important finding.

Table 1: Most Cited Articles

Rank	Article	Year	Total Citations
1	The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and sterility. 2004;81(1):19-25.	2004	3830
2	The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS), Human Reproduction. 2004;19(1):41–47	2004	3532
3	Van Steirteghem AC, Nagy Z, Joris H, Liu J, Staessen C, Smitz J, Wisanto A, Devroey P. High fertilization and implantation rates after intracytoplasmic sperm injection. Hum Reprod. 1993 Jul;8(7):1061-6.	1993	1042
4	Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011; Jul;26(7):1616-24.	2011	1036
5	Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril. 2000 Jun;73(6):1155-8.	2000	939

Information on the top five authors who published the most articles is given in **Table 2**. According to this information, it was determined that the authors published more than 100 articles, and the authors who published the most articles were Paul Devroey (n=189), Antonio Pellicer (n=152), and Zev Rosenwaks (n=139).

The findings regarding the keywords with a high frequency of use in the articles included in the analysis are given in **Table 3**. According to these findings, the terms "in vitro fertilization" (n=10637), "pregnancy" (n=2471), and "women" (n=1928) were found to be the most used keywords.

Table 2. Most Prolific Writers

Rank	Name	Number of documents
1	Paul Devroey	189
2	Antonio Pellicer	152
3	Zev Rosenwaks	139
4	Herman Tournaye	111
5	José Remohí	110

Table 3. The Most Used Keywords in the Research

Rank	Keyword	Number of Times Used
1	In vitro fertilization	10637
2	Pregnancy	2471
3	Women	1928
4	Infertility	1817
5	Embryo transfer	1780
6	Implantation	1436
7	Intracytoplasmic sperm injection	1425
8	Assisted reproductive technology	1378
9	Pregnancy rates	1344
10	Ovarian stimulation	1126

Strategic diagrams related to the themes obtained as a result of the analysis carried out are given in **Figure 3**. According to this

- 18 in the first period (7 motor themes, 3 isolated and advanced themes, 3 basic and transformational themes, 5 emerging or disappearing themes),
- 22 in the second period (8 motor themes, 4 isolated and advanced themes, 4 basic and transformational themes, 6 emerging or disappearing themes) and
- 29 in the third period (8 motor themes, 7 isolated and advanced themes, 7 basic and transformational themes, 7 emerging or disappearing themes) themes were formed.
- In the first period, 1990-1999, the most published article (n=287), the most cited (n=15750), and the highest h-index (68) was the motor theme "Implantation".
- The motor theme "Women" with the highest number of articles published (n=542), the most cited (n=24427), and the highest h-index (83) in the second period, 2000-2009,
- In the third period, 2010-2020, the motor theme with the most articles published (n=771), the most cited (n=15307) and the highest h-index (61) is the "Implantation" theme, as in the first period.

The theme of "Luteinizing hormone" maintains its importance in the first two periods and takes place as a motor theme. According to the findings on the theme of "luteinizing hormone", it was seen that 112 articles published in the 1990-1999 period received 4527 citations and the h-index value was 41, while 351 articles published in the 2000-2009 period received 14432 citations and the h-index value was 65. One of the motor themes of the first period, "Intracytoplasmic sperm injection" (number of publications: 116; a number of citations: 6541; h-index: 46) and (number of publications: 229; a number of citations: 4478; h-index: 36) in the last period was found to be included.

The "Oocyte" theme, which is included in the strategic diagrams of all periods, was the main and transformational theme in the first period (number of publications: 60; number of citations: 2978; h-index: 32), the theme that emerged or disappeared in the second period (number of publications: 94; a number of citations: 4138; h-index: 40), and recently it has been the main and transformational theme (number of publications: 157; a number of citations: 4161; h-index: 36).

The theme of "Endometrium", which emerged or disappeared in the first two periods (number of publications in 1990-1999 period: 17; a number of citations: 712; h-index: 11; a number of publications in

2000-2009: 33; a number of citations: 1330; h -index: 21) has not found a place recently.

The “Ectopic pregnancy” theme (number of publications: 9; a number of citations: 235; h-index: 8), which is among the themes that emerged or disappeared in the first period, has also emerged or disappeared in the last period (number of publications: 21; the number of citations: 297; h-index: 8) in the diagrams.

Similarly, the "Single embryo transfer" theme (number of publications: 80; a number of citations: 4200; h-index: 40), which was among the isolated and advanced themes in the second period, was followed by the basic and transformational theme (number of publications: 98; a number of citations: 2872; h-index: 29).

The theme of “Intrauterine insemination” has emerged or disappeared in the last two periods (number of publications in 2000-2009 period: 53; a number of citations: 1724; h-index: 23; a number of publications in 2010-2020: 73; a number of citations: 1793; h -index: 21).

Similarly, the theme of “Miscarriage” has emerged or disappeared in the last two periods (number of publications in the period 2000-2009: 13; a number of citations: 1021; h-index: 10; a number of publications in the period 2010-2020: 20; a number of citations: 557; h-index: 9).

According to the thematic development map findings obtained in our research,

- The "Luteinizing hormone" theme in the first two periods is in correlation to the "GNRH antagonist" theme in the last period.
- The theme of “Antral follicle count” in the second period is related to the theme of “Anti Mullerian hormone” from the last period.
- The "Implantation" themes, which have the highest number of articles in the first and last period, are related to the "Pregnancy rates" theme, which is one of the themes with the highest number of publications in the second period,
- The theme of "Human chorionic gonadotropin", one of the themes of the second period, is related to the themes of "Progesterone" from the first and last period, and the theme of "Ovarian hyperstimulation syndrome" from the last period.

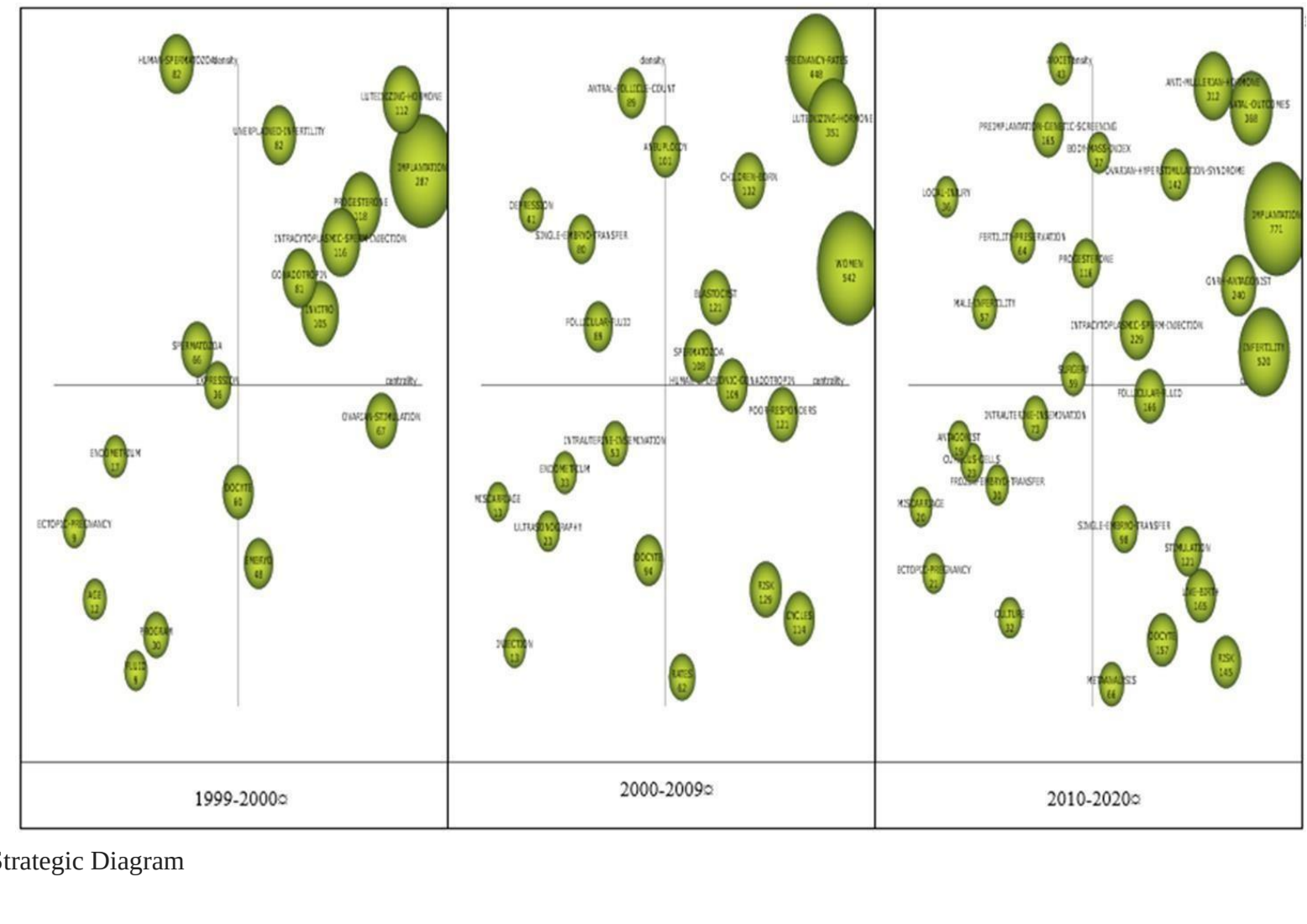

Figure 3: Strategic Diagram

Discussion

It was determined that the number of articles on IVF was few before 1990, and the number of publications increased gradually in the following years. Human reproductive research is fraught with scientific and ethical challenges that hinder the development of infertility treatments. The study of events in human oocyte fertilization gained momentum in the 1960s and 1970s, and the point at which in vitro fertilization of human oocytes was possible was reached in the late 1970s. As a result, the first live birth via IVF took place in England in 1978, with the number reaching 15 in the early '80s. This explains the fact that articles on IVF were rarely encountered in the 80s but increased in the form of an explosion in the 90s **[1]**.

According to the distribution of articles published on IVF by country, the USA stands out with 3716 articles. According to the number of articles, the USA is followed by the UK with 1044 articles and China with 861 articles. Turkey ranks 10th with 549 articles. It is seen that countries that have a say in the academic field such as the USA, England, China, India, Korea, Germany, and Japan also come to the fore in studies on IVF. When all medical publications are taken into account, while the USA, China, England, and Germany rank first in the world, Turkey ranks 16th. However, when we look at the number

of citations received by the publications belonging to the countries, Turkey is even further behind. Considering the articles published on IVF, the situation of Israel and Belgium is remarkable. When all medical publications are taken into account, Israel ranks 24-25 in the world, Belgium ranks 18th, and these two countries come to the fore when it comes to articles published on IVF. The reason for this may be that IVF treatment is cheaper in Israel compared to the rest of the world, Belgium has significant experience in IVF treatment and is preferred by surrounding countries for this treatment **[7–9]**.

According to the information on the most cited articles, the first two most cited articles were published by "The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group". Both articles are about the consensus on the diagnostic criteria and long-term health risks of polycystic ovary syndrome. The PCOS Consensus Workshop Group is a working group on polycystic ovary syndrome. It is supported by organizations called ESHRE/ASRM (European Society of Human Reproduction and Embryology / The American Society for Reproductive Medicine). The working group held its first meeting in 1990. Since then, it has regularly published guidelines on polycystic ovary syndrome. Guides are considered essential works by practitioners of the subject. It is an expected result that the version of these guidelines published in 2004 is frequently consulted and cited by researchers **[10]**.

The 1993 article published by Van Steirteghem et al. follows these articles on the citation. In this article, intracytoplasmic sperm injection is discussed in patients who cannot fertilize oocytes after standard IVF procedures or who are not accepted for IVF because there are not enough motile sperm in the ejaculate. It is one of the first published articles on this subject and the results of 150 patients are shared. It is a very interesting article in terms of its content; therefore, it has received many citations **[11]**.

Considering the period in which the article, published by Ferraretti et al. in 2011, was in the fourth place, it was evaluated that the high number of citations it received is an important finding and should be discussed. This article discusses the Bologna criteria. These criteria were published by a working group supported by the European Society of Human Reproduction and Embryology to address the lack of a clear definition of poor ovarian responders. The work, which was accepted as a reference by scientists working on the subject, received many citations as expected **[12]**.

When the information about the top five authors who published the most articles is examined, it is seen that the names Paul Devroey and Antonio Pellicer come to the fore.

Professor Devroey is a highly cited senior scientist with a very high h-index score. He has worked in the field of intracytoplasmic sperm injection. He has published many books. He is the founding president of the Belgian Society of Reproductive Medicine, the director of the Medical Education of the International Federation of Fertility Societies, and the former president of the European Society of Human Reproduction and Embryology **[13]**.

Antonio Pellicer is a senior researcher known for his work focused on infertility. He is the founding president of Instituto Valenciano de Infertilidad. He is a member of the European Society of Human Reproduction and Embryology and the International Federation of Fertility Societies **[14]**.

The Luteinizing hormone theme takes place as a motor theme in the first two periods. The theme of luteinizing hormone has been studied within the scope of articles published in the period 1990-1999 and 2000-2009. In this context, it has been seen that many studies have been carried out to better understand the physiology of folliculogenesis and the role of LH activity in the folliculogenesis process. It is one of the most frequently emphasized data obtained from these studies that externally administered luteinizing hormone improves implantation **[15–17]**.

Intracytoplasmic sperm injection is one of the motor themes of the first and last period. This issue has been brought to the attention of the academic public through studies conducted by Van Steirteghem et al. The article published by these researchers is one of the most studied articles among the articles on the subject. Intracytoplasmic sperm injection is a treatment for patients who cannot fertilize oocytes with standard IVF procedures or who are not admitted to IVF because there is not enough motile sperm in the ejaculate. The treatment attracted great attention when it was first presented to the public. However, with studies conducted in the following years, concerns about some inappropriate uses and side effects have been expressed. In the USA, since 1995, intracytoplasmic sperm injection has increased significantly, while the proportion of patients treated for male factor infertility has remained stable. This shows that intracytoplasmic sperm injection is also performed for infertility not attributed to the malefactor. In a study conducted in the same period, it was reported that the risk of major birth defects was twice as high in the babies of mothers who became pregnant with the intracytoplasmic sperm injection method compared to the babies of mothers who became pregnant naturally. The results obtained in the studies carried out in the third period, 2010-2020 results, are also similar to the results of the second period. According to the results of a study conducted, the use of intracytoplasmic sperm injection in the USA increased from 36.4 % in 1996 to 76.2 % in 2012.

Compared with traditional IVF, it has been reported that the use of intracytoplasmic sperm injection does not have a positive effect on fertility. The correlation between a birth defect and intracytoplasmic sperm injection was also confirmed by studies in this period. It has been determined that the children of mothers who became pregnant with IVF and/or intracytoplasmic sperm injection are at a significantly higher risk for birth defects **[11,18–21]**.

As a result of examining the relationships between the themes, it was determined that the theme of Human chorionic gonadotropin and the theme of Ovarian hyperstimulation syndrome from the last period were related. Ovarian hyperstimulation syndrome is the most serious iatrogenic complication of ovulation induction. It is almost always

associated with exogenous gonadotropin stimulation followed by the administration of hCG to trigger oocyte maturation. Because of this relationship, the relationship between these themes belonging to different periods has been determined **[22]**.

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