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ASSISTED REPRODUCTION TECHNOLOGIES

Fertility management in the PCOS population: results of a web-based survey at IVF-worldwide.com

Paul R. Brezina · Virginia Mensah · Adam Balen · Milton Leong · Ariel Weissman · Yulian Zhao · Zeev Shoham

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Abstract
Purpose To identify the leading treatment strategies for infertile women with PCOS on an international scale.
Methods A retrospective evaluation using the results of a web-based survey, (IVF-Worldwide (www.IVF-worldwide.com), posted from 1 to 30 September 2010 was performed. Binomial confidence intervals for proportions were calculated by the modified Wald method with significance defined as $P<0.05$ using a DataStar software package (DataStar, Waltham, MA, USA). Incomplete surveys were excluded from the analysis.

Capsule This study describes the treatment patterns for PCOS via a survey of 262 centers in 68 nations.

Results The results from 262 centers in 68 nations were obtained. Clomiphene citrate was the clear first choice, 68 %, for PCOS treatment in the respondent group. Eighty-eight percent of respondents utilized ultrasound follicular monitoring when conducting ovulation induction with oral medications. A significant ($p<0.05$) proportion of respondents (66 %) did use some BMI cutoff beyond which IVF treatment was not offered. The preferred IVF protocols for PCOS patients were gonadotropin releasing hormone (GnRH) antagonist, 46 %, and GnRH agonist, 51 %. There was heterogeneity of responses observed regarding the management of a patient at very high risk of OHSS.
Conclusions While some advances, such as the use of GnRH antagonist regimen in IVF cycles, were relatively underutilized, the survey gives an unfiltered snapshot at the practice patterns of a large number of clinics. Results from this survey may be used by researchers and professional organizations to improve the clinical care of PCOS women suffering with infertility.

Keywords PCOS · Infertility · Treatment · IVF · Survey

P. R. Brezina (✉)
Reproductive Genetics, Fertility Associates of Memphis, 80 Humpreys Center, Suite 307, Memphis, TN 38120-2363, USA
e-mail: brezinamd@gmail.com

V. Mensah
Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

A. Balen
Leeds Centre for Reproductive Medicine, Seacroft Hospital, Leeds, UK

M. Leong
IVF Centre, The Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong

A. Weissman
Department of Obstetrics and Gynecology, Edith Wolfson Medical Center, Holon, Sackler Faculty of Medicine, Tel Aviv University, IVF Unit, Tel Aviv, Israel

Y. Zhao
Department of Gynecology and Obstetrics, Division of Reproductive Endocrinology and Infertility, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Z. Shoham
Department of Obstetrics and Gynecology, Kaplan Medical Center, Rehovot, Israel

Introduction

PCOS affects approximately 5–10 % of women worldwide, and accounts for the estimated majority of cases of anovulatory infertility in the US [4,6,14]. Though its exact definition remains controversial, consensus remains that the condition is characterized by menstrual irregularities such as oligo- or anovulation, evidence of hyperandrogenism, and polycystic ovaries [4,6,14]. Treatment modalities for infertility in this patient population are varied, and historically have included behavioral health modifications including diet and exercise, ovulation induction with clomiphene citrate, metformin, gonadotropins, or aromatase inhibitors, laparoscopic electrosurgery of the ovaries, or IVF/ICSI [4,6,14]. Because of the

large range of historical and current treatments for PCOS, consensus on the most appropriate treatments for PCOS as it relates to infertility is somewhat lacking. This study attempts to identify the leading treatment practice patterns from a large number of reproductive endocrinology clinics on an international scale.

IVF-Worldwide (www.IVF-Worldwide.com) is a comprehensive IVF-focused website linking doctors and specialists in IVF centres around the world in order to encourage dialogue and discuss special treatments and medications. The website was created to promote education and has no relationships with specific products, drug companies, device companies, or any other aspects of industry. With the use of this internet-based survey tool, this study attempted to determine the most commonly utilized practice patterns utilizing to treat infertile women with a diagnosis of PCOS.

Materials and methods

Johns Hopkins Institutional Review Board (IRB) determined that the research does not involve human subject research under the regulations of the Department of Health and Human Services or the Food and Drug Administration. Consequently, formal IRB approval was not obtained. The web-based questionnaire entitled 'PCOS – definition, diagnosis and treatment' was posted on the IVF-Worldwide website on 1 September 2010 and was closed on 30 September 2010. The survey contained demographic questions including the name of the clinic's medical director, the name of the IVF unit, email address, country and number of IVF cycles performed in the unit in the most recent year. The survey evaluated the practice patterns and opinions of respondents with a series of 'yes' or 'no' and multiple-choice questions.

Quality assurance methods

In order to minimize duplicate reports from a unit and possible false data, computerized software assessed the consistency of four parameters in the self-reported data of the unit surveyed with existing data of units registered on the IVF-Worldwide website. These parameters included the name of the unit, the name of the unit director, the country and its email address. If at least three of these parameters from the survey matched the website archive data, this reporting site's data were included in the statistical analyses.

Data evaluation

The raw data used in this study, which have been not publicly available prior to this publication, were uploaded into a computerized spreadsheet using Excel (Microsoft, Redmond CA, USA). Binomial confidence intervals for proportions were calculated by the modified Wald method with significance defined as $P<0.05$ using a DataStar software package (DataStar, Waltham, MA, USA). For each question, if there was one answer choice that was significantly higher than all other answer choices as determined by an individual binomial confidence interval for proportions, this was noted as statistically significant. Incomplete surveys were excluded from the analysis.

Results

The results of the survey including the questions asked in the survey and corresponding responses are given in Tables 1–10. Of 309 respondents that initially began the survey, 47 failed to complete the survey and were excluded. Therefore, final surveys were evaluated from 262 centres in 68 nations. Each clinic performed an average of 684 (range 100–4500) IVF cycles annually. The global distribution of clinics (outlined in table 12) was: Europe, 87 clinics (33 %); Asia, 62 clinics (24 %); South America, 56 clinics (21 %); USA/Canada, 33 clinics (13 %); Africa, 13 clinics (5 %); and Australia, 11 clinics (4 %). The self-reported number of cycles performed by each fertility center, by region, is shown in Table 11. The vast majority (92 %) of all respondents stated that they used the Rotterdam criteria to diagnosis PCOS.

When asked what is the best first line treatment for PCOS, a significantly higher, as compared to other answer choices, ($p<0.05$) percentage of respondents (68 %) use clomiphene citrate with or without metformin and followed with ultrasound monitoring (88 % of respondents) (Tables 1, 2). Only 5 % of respondents used no monitoring when conducting an ovulation induction cycle using clomiphene citrate (Table 2).

Table 1 In case of primary infertility in anovulation PCOS patient what is your first line of treatment?

Preferred treatment modality	Percentage response
Metformin for all with no O.I. drugs	6 %
Metformin to those who are diagnosed with insulin intolerance	12 %
CC with or without Metformin	68 %*
Aromatase inhibitors with or without Metformin	8 %
Gonadotropins with or without Metformin	5 %
IVF with or without Metformin	1 %
IVM with or without Metformin	0 %
Laparoscopic cauterization/ovarian drilling	0 %

*Response that was significantly higher ($p<0.05$) than all other individual answer choices

CC Clomiphene citrate; *O.I.* Ovulation induction

Table 2 If you use clomiphene citrate do you monitor with

Preferred treatment modality	Percentage response
Ultrasound	59 %*
Ultrasound plus luteal phase progesterone measurement	14 %
Ultrasound plus Estrogen plus luteal phase progesterone measurement	15 %
Luteal phase progesterone measurement	6 %
No monitoring	5 %

*Response that was significantly higher ($p<0.05$) than all other individual answer choices

When gonadotropins were used, the most common as compared to other answer choices, 60 % of respondents, ($p<0.05$) dosing protocol was a low dose step-up protocol.

A significantly higher, as compared to other answer choices, ($p<0.05$) proportion of respondents (66 %) did use some BMI cutoff beyond which IVF treatment was not offered (Table 3). In patients in whom IVF is appropriate, 55 % of respondents initiated Metformin therapy orally prior to beginning the treatment cycle (Table 4). The preferred IVF protocols for PCOS patients were gonadotropin releasing hormone (GnRH) antagonist, 46 %, and GnRH agonist, 51 % (Table 5). Thirty-nine percent of respondents report using only follicle stimulating hormone (FSH) exclusively to induce controlled ovarian hyperstimulation (COH) and generally, 59 % of respondents, at a dose of 150 international units (IU) daily (Table 6, 7).

The participants of this survey noted significant exposure to treating PCOS patients with 86 % of respondents noting the percentage of PCOS patients in their practice exceeding 10 % of their general patient pool (Table 8). Twenty-one percent of respondents reported that more than 20 % of their patients are diagnosed with PCOS (Table 8). In the opinion of 72 % of respondents, the ultimate chance of achieving pregnancy in PCOS was as good as or better than that of their general infertility patient population (Table 9). When asked how a patient at very high risk for developing ovarian hyperstimulation syndrome (OHSS) was optimally treated during an IVF stimulation cycle, respondents preferred a variety of strategies to diminish the chances of OHSS (Table 10).

Table 3 Is there a limit to BMI above which you will not gibe IVF treatment?

Preferred treatment modality	Percentage response
NO, we do not stop treatment in any case, related to obesity	34 %
BMI above 30	11 %
BMI above 35	31 %
BMI above 40	19 %
BMI above 45	5 %

Table 4 Do you treat Metformin (Glucophage) before starting the IVF treatment (for at least on month)?

Preferred treatment modality	Percentage response
Yes	55 %*
No	45 %

*Response that was significantly higher ($p<0.05$) than all other individual answer choices

Discussion

The results from this large survey offer key insights into how PCOS is currently managed by reproductive specialists. Clomiphene citrate was the clear first choice, 68 %, for PCOS treatment in the respondent group. The use of aromatase inhibitors (AI) was only 8 %. This is interesting as AIs have been promoted by some as especially advantageous in ovulation induction of the PCOS patient [2,7,10]. Even though AIs appear to be safe in terms of fetal teratogenic risks [15], Novartis, the producer of Letrozole, states that it is only indicated for postmenopausal women and it is contra-indicated in women who may become pregnant (http://www.pharma.us.novartis.com/product/pi/pdf/Femara.pdf). It is likely that many physicians are refraining from the off-label use of Letrozole for ovulation induction. There are countries (Israel and India for example) where the off-label use of AIs for ovulation induction is forbidden. These considerations may explain the relative limited use of AIs for ovulation induction worldwide. However, the use of AI is not uncommon currently in many parts of the world. Determining how AI are currently used, however, may be problematic as

Table 5 Would you prefer to do IVF using GnRH agonists, GnRH antagonists, natural cycle or IVM

Preferred treatment modality	Percentage response
In most of the cases I use GnRH agonists	34 %
In most of the cases I use GnRH antagonists	46 %
I prefer to start with the OC pill and continue with GnRH agonist	17 %
I prefer Natural cycle	1 %
In most of the cases I do IVM	1 %
None of the above	2 %

Table 6 Which drug do you use for stimulation in IVF?

Preferred treatment modality	Percentage response
I use CC with gonadotropins	2 %
I use FSH only (recombinant FSH)	39 %*
I use FSH and add LH if necessary (recombinant drugs)	18 %
I always start with a combination of FSH and LH (recombinant drugs)	4 %
I always start with FSH and add mini dose of hCG	5 %
I always use hMG	9 %
I use different protocols with different stimulation drugs	23 %

*Response that was significantly higher ($p<0.05$) than all other individual answer choices

there are often differences in practice patterns between private/public institutions. The use of AIs were reported in all regions evaluated in this study. However, the relatively low percentage of those reporting the use of this approach as a 1st line (8 %) precluded meaningful statistical analysis of geographic distribution.

Over the past decade, however, there does seem to be increasing use of AI for ovulation induction by reproductive physicians with over 100 publications on this topic published since 2005 [3]. Currently in the United States, several large randomized multicenter studies by clinics in the National Institute of Child Health and Human Development (NICHD) Reproductive Medicine Network are ongoing that directly compare outcomes of women treated with clomiphene citrate versus AI for ovulation induction [3]. One would assume that if there were serious concerns regarding the safety of AI for this purpose, such studies would be exceedingly difficult to be approved by the numerous institutional IRB committees necessary for such a project.

Also interesting is that among reproductive specialists, ovulation induction was closely monitored with the vast majority, 88 %, of respondents using ultrasound monitoring during such cycles. This is in sharp contrast to the application of oral ovulation induction agents without ultrasound monitoring practiced by many general practice physicians [5,16].

Table 7 What dose of gonadotropin you usually start in IVF cycles?

Preferred treatment modality	Percentage response
I do not reduce the starting dose in PCOS patients	6 %
I usually start with 150 IU of FSH and in PCOS patients I reduce the dose to be in between 75 to 150 IU	59 %*
I usually start with 225 IU of FSH and in PCOS patients I reduce the dose to be in between 150 to 225 IU	19 %
None of the above	15 %

*Response that was significantly higher ($p<0.05$) than all other individual answer choices

Table 8 Can you estimate the percentage of PCOS patients in your clinic?

Preferred treatment modality	Percentage response
Less than 10 %	14 %
Less than 10–15 %	33 %
Less than 15–20 %	32 %
More than 20 %	21 %

Also of interest is that the majority of practitioners (66 %) do have BMI cut-offs in place above which IVF will not be offered. Grossly elevated BMIs have been documented to correlate with decreased pregnancy rates and poorer pregnancy outcomes. [8,11,18] Although some data suggest the quality and number of oocytes is similar in patients with different BMIs [13], obesity and elevated BMI have been associated with decreased oocyte retrieval and increased miscarriage rate following use of assisted-reproductive technology [9,12]. Therefore, this observation is consistent with an appropriate practice modification by many practitioners.

Only 46 % of respondents preferred using a GnRH antagonist based cycles for PCOS patients while 51 % still use GnRH agonist based cycles. This is interesting as a principal rationale for the use of GnRH antagonist based cycles is to minimize the incidence of OHSS, a condition for which PCOS patients are at high risk [17]. It is unclear as to the reasons GnRH antagonist based cycles for PCOS patients were not represented at a higher proportion. Existing data is conflicting in regards which cycle model (GnRH antagonist versus agonist cycles) is superior in regards to pregnancy rates [1]. However, data does clearly show lower rates of OHSS with GnRH antagonist cycles [17]. Now, that more data has accumulated on the safety and efficacy of GnRH antagonist based protocols in PCOS patients undergoing ART, their use should be advocated through updated consensus communications.

Table 9 Can you estimate the pregnancy rate among these patients in comparison to the other population you treat?

Preferred treatment modality	Percentage response
No change in pregnancy rate	42 %*
Lower pregnancy rate	29 %
Higher pregnancy rate	30 %

*Response that was significantly higher ($p<0.05$) than all other individual answer choices

Table 10 In case of finding on the day of hCG an ultrasound scan in which the ovaries contain around 30 follicles in between 12 mm and 25 mm in diameter (in both ovaries), and estradiol level of 8000 pg/ml (29,000 pmol/l) what would you do?

Preferred treatment modality	Percentage response
Go ahead with hCG and aspirate the follicles	3 %
Administer 0.5 of the usual dose of hCG and go ahead with aspiration	2 %
Give hCG and aspirate the follicles and give albumin	2 %
Administer 0.5 of the usual dose of hCG and go ahead with aspiration and give albumin	3 %
Costing until the estradiol level decrease to the usual range in my unit	19 %
Cancel the cycle	18 %
Aspirate the eggs, freeze any embryos created and avoid fresh transfer	16 %
Aspirate the eggs, give albumin, freeze any embryos created and avoid fresh transfer	11 %
Administer dopamine agonists and continue with IVF	7 %
Other not specified above	18 %

Of particular interest in this survey was the heterogeneity of responses observed regarding the management of a patient at very high risk of OHSS. This question was designed to gauge the management decisions of women on a GnRH agonist cycle and therefore the option of using a GnRH agonist trigger in the context of a GnRH antagonist cycle was not given. Admittedly this is a limitation of the survey as 46 % of respondents preferred using a GnRH antagonist based cycles for PCOS patients and would have likely used such a strategy for diminishing the likelihood of OHSS. Appropriately, 97 % of respondents stated that they would make some modification to decrease the incidence or severity of OHSS. Coasting or cancelling the cycle were the two most commonly used strategies, 37 %.

This survey appears to be the largest study to date evaluating the practice patterns surrounding the treatment patterns used to clinically diagnose PCOS worldwide. However, while this survey does pull respondents from an international pool, certainly this data is subject to a selection bias as only those who are familiar with the website would or could have participated. Therefore, it would be inaccurate to presume that this data necessarily reflects global practice patterns. Indeed, even within individual countries, practice patterns may significantly vary. Despite these limitations, this survey does offer a snapshot of practice patterns simultaneously in many geographically, ethnically, and culturally diverse regions of the world.

The model of this survey is a significant departure from the traditional approach of gauging provider practice patterns. Specifically, this survey was not sent directly to providers but was instead available on an open-access basis. This introduces multiple sources of bias and error that may not exist via other data gathering tools. In many nations, certain data, such as IVF success rates, are legally mandated to be reported leading to high quality metrics for certain clinical questions. In other instances, surveys are sent to specific individuals to obtain data regarding practice patterns and trends. These traditional methods are thought to be high quality approaches for obtaining such data as the respondents are known and are accountable for the data provided. However, even in these instances, independent validation of the data provided is very rarely exercised. Additionally, these approaches, because they are tied to reporting of specific individuals, may introduce an incentive to represent data in ways that accentuate the positive attributes of particular individuals or clinics.

The novel approach utilized in this survey was developed to gauge the practice patterns of clinics worldwide on a large scale. In this respect, this survey model was successful as the survey captured the practice patterns of 262 centres from 68 countries and 5 continents, a goal that would be very difficult using a traditional survey model. Table 11 shows the geographic distribution of survey respondents both in the number of centers and the volume of IVF cycles reported by these regions. The geographic distribution of survey respondents, outlined in Table 11, were a similar when evaluating the number of centers and after adjusting for the number of IVF cycles performed by these centers. This minimizes the chances that very large centers in several countries could significantly skew the outcome data.

Table 11 Shows the geographic distribution of survey respondents both in the number of centers and the volume of IVF cycles reported by these regions

	Number of estimated annual IVF cycles	Number of centers responding to survey	Percentage of estimated annual IVF cycles	Percentage of centers responding to survey
USA/Canada	27500	33	15 %	13 %
South America	38800	56	22 %	21 %
Australia	7900	11	4 %	4 %
Asia	41300	62	23 %	24 %
Europe	55400	87	31 %	33 %
Africa	8400	13	5 %	5 %

While the methodology of this survey did result in a large sample size, there are several concerns that exist regarding the application of this survey's results to the widespread medical community. Specifically, the centres that entered data volunteered to participate and therefore an inherent self-selection bias may be present in this data. Much like traditional surveys, participants in this survey were required to provide specific identifiers. Specifically, all surveys reported the name and location of the IVF clinic as well as the name of the clinic's medical director. This served several functions. Firstly, this approach assigned a responsible party to all data entered on the survey. Additionally, this approach attempted to ensure that duplicate data would not be provided multiple times from the same centers as this would be easily identified at the time of data analysis. Of note, no instances of such multiple entries were identified. However, this mechanism cannot completely eliminate the possibility that the survey tool could have been manipulated by respondents to generate duplicate responses.

It is also possible that respondents could have "made up" erroneous responses for survey questions. However, from a practical point of view, this same criticism could be made for many other survey tools as independent post response validation of practices based on survey responses is rarely if ever performed. An additional bias of the survey could be that because the survey was not blinded, some respondents may be reluctant to disclose off label use of medications such as AI for ovulation induction. In this regard, a blinded survey tool may be even more accurate in gauging actual treatment patterns.

Additionally, a series of questions with a finite number of answer choices, are inherently inadequate to fully capsulate the practice pattern of an entire clinic. Furthermore, this survey was retrospective in nature, relying on those completing the survey to make estimates of their practice patterns rather than derive their practice patterns from objective patient data.

However, the strengths of this study, including its relatively large sample size and global reach, are worthy of discussion and may reflect aspects of PCOS treatment that deserve further attention. The data represented in this paper support the contention that practitioners worldwide provide thoughtful and appropriate medical care to women who suffer from PCOS and desire pregnancy. While some advances, such as the use of GnRH antagonist cycles in IVF cycles, were relatively underutilized, the survey gives an unfiltered snapshot at the practice patterns of a large number of clinics. Results from this survey may be used by researchers and professional organizations to improve the clinical care of PCOS women suffering with infertility.

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