Metformin use in patients undergoing in vitro fertilization treatment: results of a worldwide web-based survey

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Received: 1 September 2014 / Accepted: 18 December 2014 / Published online: 30 January 2015
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Abstract

Purpose To identify trends regarding therapeutic approaches to metformin administration in patients undergoing in vitro fertilization (IVF) treatment worldwide.

Methods A retrospective evaluation utilizing the results of a web-based survey, IVFWorldwide (www.IVF-worldwide.com/), was performed.

Results Responses from 101 centers performing a total of 50,800 annual IVF cycles was performed. Of these cycles, 10.4 % ($n=5,260$) reported metformin use during IVF cycles. Indications for metformin use in IVF cycles included polycystic ovary syndrome (PCOS) patients who were habitual abortions (67 %), had prior poor egg quality (61 %), had high serum insulin levels (56 %). Less reported was PCOS with obesity/anovulation (29 %), PCOS with multiple manifestations (23 %) and glucose intolerance and insulin resistance (23 %). Over half of cycles (54 %) treated patients with metformin up to 3 months prior to starting IVF. A majority (82 %) of IVF cycles utilized 1500–2000 mg/day of metformin. A nearly equal percentage of centers continued metformin up to a positive β -HCG test

(35 %) or to 12 weeks gestation (33 %). 70 % of IVF cycles reported increased pregnancy rates and decreased miscarriage rates due to the use of metformin. 75 % reported the data in the literature is not sufficient for reaching a definitive conclusion concerning metformin treatment in patients undergoing IVF.

Conclusions While metformin is used worldwide as an adjunct to standard IVF protocols, there is much variation in its use and the majority of centers report lack of evidence supporting its use.

Keyword Metformin · Polycystic ovary syndrome · In vitro fertilization · Assisted reproductive technology

Capsule There is much variation in use of metformin in IVF cycles worldwide.

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Introduction

For patients with polycystic ovary syndrome (PCOS), insulin resistance has been recognized as a key contributor to the pathophysiology of the disease. Given the role of insulin resistance in PCOS, insulin-sensitizing drugs have received much attention for infertility treatment in this population. Metformin, a biguanide oral anti-hyperglycemic agent, has been widely studied in the last 15 years. It decreases blood glucose levels by enhancing peripheral glucose uptake, decreasing intestinal glucose absorption and suppressing hepatic glucose levels. Metformin has multiple established and developing applications in women's reproductive health, including PCOS [1]. In anovulatory women with PCOS, the drug decreases insulin levels, luteinizing hormone (LH) production and circulating androgen levels [2]. When used for ovulation induction in PCOS patients, metformin has been found to increase ovulation and clinical pregnancy rates [3]. Though the drug alone is not superior to the ovulation induction agent clomiphene citrate (CC), it improves fertility outcomes in CC-resistant women [3–5]. This combination therapy of

metformin and CC is also effective in improving fertility in obese patients with PCOS [6].

Due to the potential fertility benefits of metformin, it has become increasingly common practice for clinicians to administer or continue metformin therapy in patients undergoing in vitro fertilization (IVF) [7]. Studies to date have demonstrated mixed results for metformin administration in PCOS patients undergoing IVF treatment with respect to reproductive outcomes. These studies displayed considerable heterogeneity in terms of patient characteristics, treatment protocols and study settings [8–20]. Thus, there is currently a significant degree of uncertainty for the specific role of metformin in IVF therapy. Furthermore, therapeutic regimens and treatment protocols for metformin administration are not well-standardized in clinical practice [21].

IVF-Worldwide (www.IVF-Worldwide.com) is a comprehensive IVF-focused website for physicians, embryologists, nurses and social workers. The website allows members to locate IVF centers anywhere in the world to communicate directly, facilitating the sharing of ideas and discussion of treatments and medications. The non-commercial, non-profit website with an advisory panel of 52 leaders in the fertility field routinely performs surveys focusing on various aspects of ART.

The purpose of our web-based survey was to identify trends regarding therapeutic approaches to metformin administration in patients undergoing IVF treatment, and to correlate these results with current evidence-based literature. This information may prove useful to providers seeking guidance in metformin administration as part of fertility treatment protocols, especially for PCOS patients.

Materials and methods

An 18-item survey entitled “Metformin Use in IVF Patients” was compiled and posted on the IVF-Worldwide website from December 2009 to January 2010. Please refer to the questions stems in Appendix A. The survey recorded demographic information including the name of the IVF unit and its medical director, e-mail address, country, number of IVF cycles performed by the unit in the past year, and the number of those cycles that involved metformin treatment. Survey questions focused on various aspects of metformin administration in patients, including indications for metformin use, laboratory studies prior to treatment, and details of treatment protocols including timing, dosage, formulations, laboratory monitoring and treatment duration. Attitudes of IVF units were also assessed regarding the observed impact of metformin on reproductive outcomes, the association between metformin and gonadotropins, and the sufficiency of data in the literature regarding

metformin use. This study was determined to be exempt from institutional review board approval by Johns Hopkins University School of Medicine.

Quality assurance methods

Minimization of duplicate reports from a unit as well as possible false data was achieved via a computerized software program that assessed the consistency of four parameters from 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, name of the unit director, country, and e-mail address. At least three of the parameters from the survey had to match archived data on the website in order for the reporting site’s data to be included as part of the study.

statistical analysis

Analysis of responses was based on the reported number of IVF cycles and not by the number of units who responded to the survey. For each question, the survey provided single-answer multiple choice questions (via ‘radio buttons’). After approximately 10 weeks, data was collected from 5,260 IVF cycles and this sample size was considered sufficient.

Results

A total of 101 IVF centers from 44 countries responded to the survey and met the computerized system’s quality assurance standards. Overall, 50,800 cycles were reported. Of these cycles, 10.4 % ($n=5,260$) reported metformin use during IVF cycles and were analyzed in this study. International representation of the cycles was diverse: 38.2 % Europe ($n=2010$), 27.8 % Asia ($n=1460$), 17.7 % North America ($n=930$), 12.0 % South America ($n=630$), 2.5 % Africa ($n=130$) and 1.9 % Australia and New Zealand ($n=100$).

When asked to report indications for metformin use in IVF cycles, common patient diagnoses included PCOS patients who were habitual abortions (67 %, $n=3498$), had prior poor egg quality (61 %, $n=5260$) or who had high serum insulin levels (56 %, $n=2962$). Table 1 summarizes the commonly reported indications. Less reported diagnoses were PCOS with obesity/anovulation (29 %, $n=1531$), PCOS with multiple manifestations (23 %, $n=1220$) and glucose intolerance and insulin resistance (23 %, $n=1210$). Fewer cycles involved patients who were solely anovulatory (15 %, $n=779$), obese (5 %, $n=258$), or who showed clinical or biochemical signs of hyperandrogenism (5 %, $n=258$).

Table 1 Common clinical indications for metformin use during in vitro fertilization

Clinical indication	Number of cycles	% of Total IVF cycles with metformin
PCOS and obese	1530	29
PCOS and poor egg quality	3220	61
PCOS with habitual abortion	3500	67
PCOS with multiple manifestations – obese, anovulatory, insulin resistance, and clinical or biochemical signs of hyperandrogenism	1220	23
Glucose intolerance/insulin resistance	1210	23
High insulin levels	2960	56

There was substantial variation in laboratory studies obtained prior to metformin treatment. Among these cycles, diagnostic studies relating to glucose metabolism included glucose and insulin ratios (28 %, $n=1462$), glucose tolerance tests (24 %, $n=1252$), and fasting glucose tests (14 %, $n=720$); in approximately one-third of the cycles (34 %, $n=1831$), none of the above tests were performed. While almost half (48 %, $n=2509$) did not assess other parameters unrelated to glucose metabolism, some cycles utilized the following studies: kidney and liver function (23 %, $n=1210$); kidney and liver function with white blood cell count (WBC) (9 %, $n=452$); liver function (9 %, $n=457$); kidney function (2 %, $n=110$); vitamin B12 and folic acid (1 %, $n=58$); kidney and liver function with WBC, B12, and folic acid (1 %, $n=68$); other (7 %, $n=389$).

Timing and dosing of metformin in IVF was quite variable among survey respondents. Over half of cycles (54 %, $n=2867$) treated patients with the medication up to 3 months prior to starting IVF. Significantly fewer cycles (7 %, $n=378$) began metformin at stimulation protocol initiation. Pretreatment of only 1 month occurred in 35 % of the cycles, $n=1820$, as did starting the drug at the same time as gonadotropin releasing hormone (GnRH) analogue initiation during a long protocol. An overwhelming majority (82 %, $n=4329$) of IVF cycles prescribed 1500–2000 mg/day of metformin while 7 % ($n=868$) used below 1500 mg/day and only 1 % ($n=58$) used above 2000 mg/day. More than half (60 %, $n=3161$) reported gradually increasing the dose. Of note, 34 % of respondents, $n=1788$, indicated that they thought metformin use decreased gonadotropin consumption during stimulation. The slow-release formulation was used most frequently (78 %, $n=4108$).

Duration of metformin treatment after achieving pregnancy varied among centers. While 35 % of cycles continued metformin up to a positive β -HCG test (35 %, $n=1873$), 33 % ($n=1731$) continued to 12 weeks gestation. Other centers

continued the drug until a positive fetal heart rate (15 %, $n=810$), the end of the second trimester (5 %, $n=242$), or delivery (12 %, $n=610$). In cases in which patients did not conceive with IVF cycles using metformin, a majority (69 %, $n=3629$) of the cycles did not limit the duration of metformin treatment while 31 % ($n=1631$) had a 6-month limit for total treatment duration. The majority, 82 % ($n=4313$), did not monitor blood glucose levels while the patient was taking metformin.

In terms of treatment outcomes, 70 % of IVF cycles ($n=3682$), reported increased pregnancy rates due to the use of metformin; of these respondents, about 34 % have documented this within their centers. A majority of cycles (70 %, $n=3682$) also noted that metformin may reduce the rate of miscarriage with 36 % ($n=1894$) reporting certainty with this finding. Finally, 75 % of cycles ($n=3945$), reported that the data in the literature is not sufficient for reaching a definitive conclusion concerning metformin treatment in patients undergoing IVF.

Discussion

To our knowledge, this is the only study to date addressing the practices among an international cohort of fertility centers regarding the use of metformin in IVF patients. The survey identifies many common practices, as well as variable approaches, in metformin administration during IVF. Though a large majority of respondents believe the literature lacks sufficient data regarding metformin use in IVF treatment protocols for PCOS patients, findings from recent published studies provide insight on the clinical effect of metformin in this treatment population.

In our survey, 70 % of respondents reported that the use of metformin generally increased the rate of clinical pregnancies in IVF patients with PCOS. Alternatively, the literature reveals variable findings with respect to reproductive outcomes in this group. Tang et al. (2006) conducted one of the first large studies evaluating the effect of metformin on IVF treatment in PCOS patients. It was a randomized, placebo-controlled double-blind study involving 101 cycles. They found no difference in the gonadotropin dose required, number of oocytes retrieved or overall fertilization rates. However, there was a statistically significant higher clinical pregnancy rate (38.5 % versus 16.3 %, $p=0.02$) and pregnancy rate per embryo transfer (44.4 % versus 19.1 %, $p=0.02$) in the metformin group. There was also a significant decrease in ovarian hyperstimulation syndrome (OHSS), with 3.8 % in the metformin group versus 20.4 % with placebo ($p=0.02$) [16]. A double-blind randomized controlled trial by Kjotrod et al. (2011) explored the effect of metformin in 150 non-obese women with PCOS ($BMI < 28 \text{ kg/m}^2$) undergoing IVF therapy. Subjects were treated with metformin for 12 weeks or more prior to the cycle start. Among IVF-treated women,

there was no difference in clinic pregnancy rate between metformin and placebo groups. However, due to spontaneous pregnancies that occurred prior to IVF, there was a significantly higher clinical pregnancy rate (50 % versus 33.3 %, $p=0.04$) and live birth rate (48.6 % versus 32.0 %, $p=0.04$) in the metformin group [13]. Interestingly, in a previous double-blind randomized control trial performed by the same group in which PCOS patients were stratified by weight, there were no differences between pregnancy and live birth rates in the metformin versus placebo groups among all patients. For normal weight subjects, clinical pregnancy rates were significantly higher for the metformin group (67 % versus 33 %, $p=0.06$) [14].

Palomba et al. (2013) performed a systematic review and meta-analysis of ten randomized controlled trials evaluating metformin use in IVF therapy for PCOS patients, with an overall subject population of 845. They found that metformin administration had no effect on clinical pregnancy rate (OR 1.2, 95 % CI 0.90–1.61) or live birth rate (OR 1.7, 95 % CI 0.85–3.34). Metformin was associated with a reduced risk of OHSS (OR 0.27, 95 % CI 0.16–0.46). Additionally, miscarriage risk was reduced in the metformin group (OR 0.50, 95 % CI 0.3–0.83) [21]. This finding correlates with our survey results, in which 70 % of IVF cycles reported that metformin reduced miscarriage rates. A recent Cochrane review evaluated the safety and efficacy of metformin during IVF treatment in patients with PCOS. They found that when metformin was compared to placebo or no treatment, the metformin group had higher clinical pregnancy rates (OR 1.52, 95 % CI 1.05–2.15) but there was no clear evidence of an increase in live birth rates. Risk of OHSS was lower in the metformin group (OR 0.29, 95 % CI 0.18–0.49) [22]. In light of the findings of the meta-analyses and individual studies, the effect of metformin on IVF treatment outcomes in PCOS patients is likely variable, depending to an extent on the patient's clinical phenotype.

The survey study also revealed notable variability in metformin treatment regimens and protocols when used with IVF therapy. The medication is started from as early as 3 months prior to the IVF cycle, to as late as the beginning of ovarian stimulation, with over half (54 %) of cycles using the 3-month pretreatment protocol. Among the IVF cycles analyzed, the timing for metformin cessation in patients who conceived ranged from the point of a positive pregnancy test to as late as the delivery stage. The two most common endpoints are a positive pregnancy test (35 %) and at 12 weeks gestational age (33 %). This trend in the variability of pretreatment (if any) and treatment duration seems to be mirrored by various major studies as well—ranging from ≥ 16 weeks to the beginning of ovulation induction

for the starting time of metformin, and from hCG administration to the 12th week of pregnancy for the stopping time [10–19]. However, analysis shows no significant effect on pregnancy and live birth rates among PCOS patients after these studies were categorized by long term pretreatment (>3 weeks), short term pretreatment (≤ 3 weeks), or no pretreatment, and by stopping time of metformin with hCG administration, oocyte retrieval and embryo transfer as endpoints [21]. A significant effect was observed when metformin was administered until 12 weeks of pregnancy, but the data was only obtained in one study [17, 21]. Metformin dosages reported in our survey were similar to those used in current clinical research. We reported that 87 % of cycles prescribe between 1500 and 2000 mg/day of metformin. Similar dose distribution was also demonstrated among various major randomized controlled trials, with the majority using between 1500 and 2000 mg/day of metformin [10–19]. Regardless, in Palombo's meta-analysis, when the studies were stratified by high dose (>1000 mg/day) and low dose (≤ 1000 mg/day) treatment regimens, there was no significant difference in reproductive outcomes in PCOS women [21].

Strengths of this study are the comprehensive nature of the survey focusing on several aspects of metformin administration in IVF cycles, ranging from clinical indications to treatment protocols to perceived impact on patient outcomes. An additional strength is the large number of IVF centers and cycles represented, as well as diversity in the geographic locations represented. Our study exhibits weakness as well in that there is the potential for selection bias. Units that chose to participate in a worldwide survey may have different practice techniques than other centers worldwide that chose not to participate.

Our study demonstrates that metformin is used worldwide as an adjunct to standard IVF protocols, especially in PCOS patients. While this is not surprising given that insulin resistance is a key player in the pathophysiology of the disease, clinical research to date has not demonstrated an effect on pregnancy or live birth rates. It is noteworthy that, per the international consensus from the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), metformin administration should be restricted solely to patients with glucose intolerance and signs of insulin resistance [7]. While the most comprehensive meta-analysis on the topic to date reported that metformin exerts no clinical effect on pregnancy and live birth rates in PCOS patients, the medication shows promising results depending on the specific treatment outcomes or patient populations assessed. Equally important among the survey findings

is the substantial variation apparent in metformin regimens and treatment protocols among IVF centers worldwide. Interestingly, this variation was also quite predominant among published studies, whose outcome data observed a benefit to certain treatment algorithms but not others. This speaks to the fact that metformin use in IVF therapy is not yet well standardized in clinical practice. Further studies are needed to elucidate the effects of metformin in women undergoing IVF.

Appendix A

Table 2 Question stems used in the survey “Metformin use in IVF patients”

Question number:	Question stem:
1	Please describe patients who will receive metformin in your unit:
2	Do PCOS and poor egg quality serve as indications for the use of metformin in the next IVF cycle?
3	PCOS with habitual abortion: Is this an indication to use metformin during an IVF cycle?
4	Is high insulin an indication for use of metformin in IVF?
5	Do you perform any glucose blood test before deciding on treatment with metformin?
6	If you look for glucose:insulin ratio, what do you consider abnormal?
7	When do you start metformin treatment with respect to the IVF cycle?
8	What dosage of meformin do you prescribe?
9	Do you gradually increase the dose of metformin?
10	Do you monitor glucose while treating the patients with metformin?
11	Do you prescribe the regular or slow-release metformin?
12	Before starting treatment, apart from glucose do you look at any other specific blood tests related to the metformin administration?
13	Metformin is included in pregnancy category B, based on the FDA report, and is not expected to be harmful to an unborn fetus. Until what stage in pregnancy do you continue treatment?
14	Do you think that there is any association between metformin and gonadotropin administration?
15	What is your experience with respect to metformin in relation to pregnancy rate?
16	What is your experience with respect to metformin in relation to miscarriage rate?
17	Is there a limit to the duration of treatment with metformin if the patients do not conceive?
18	Do you think that the data available in the literature is satisfactory?

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