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ALGORITHM OF OVULATION INDUCTION IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

ALGORITAM INDUKCIJE OVULACIJE KOD PACIJENTKINJA SA SINDROMOM POLICISTIČNIH JAJNIKA

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Summary

Introduction. Polycystic ovary syndrome is the most frequent endocrine disturbance in the reproductive period of women's life and the most frequent cause of anovulatory infertility. Ovulation and pregnancy in patients having polycystic ovary syndrome may be a result of a wide range of therapeutic options, and the treatment assumes a gradual approach – from simple noninvasive to expensive and demanding procedures. **Material and Methods.** A systematic literature survey concerning the efficiency of particular ovulation induction methods in respect of the reproductive outcome was carried out with the aim of establishing the algorithm for ovulation induction in infertile patients having polycystic ovary syndrome. The search was confined to clinical investigations performed on human subjects, reported in English in the period from the beginning of 2010 to June of 2014. **Conclusion.** As a conclusion of this systematic survey of the efficiency of ovulation induction methods, which confirms and supplements the knowledge in this field, it is possible to form the algorithm for ovulation induction in infertile patients having polycystic ovary syndrome, consisting of the following subsequent steps: 1) modification of life style, 2) induction with clomiphene citrate 3) use of metformin, 4) use of aromatase inhibitors, 5) application of gonadotropins and laparoscopic ovarian drilling – as a second-line treatment, and 6) assisted reproductive techniques.

Key words: Ovulation Induction; Polycystic Ovary Syndrome; Algorithms; Treatment Outcome; Anovulation; Infertility, Female; Life Style; Clomiphene; Metformin; Aromatase Inhibitors; Gonadotropins; Laparoscopy; Reproductive Techniques, Assisted

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in the women's reproductive period, the most frequent cause of hyperandrogenism, oligoanovulation and the anovulatory infertility [1, 2]. Metabolic disorders (obesity, insulin

Sažetak

Uvod. Sindrom policističnih jajnika predstavlja najčešći endokrini poremećaj u reproduktivnom periodu žena, najčešći uzrok anovulatornog infertiliteta. Ostvarivanje ovulacije i trudnoće kod ovih pacijentkinja može biti rezultat primene širokog spektra terapijskih opcija, tako da tretman predviđa postepen pristup – od jednostavnijih, neinvazivnih do skupih i zahtevnih procedura. **Materijal i metode.** Sproveden je sistematičan pregled literature o efikasnosti pojedinih metoda indukcije ovulacije u odnosu na reproduktivni ishod radi utvrđivanja algoritma indukcije ovulacije za lečenje infertiliteta kod pacijentkinja sa sindromom policističnih jajnika. Pretraga je ograničena na klinička istraživanja sprovedena isključivo na ljudskim subjektima, objavljena na engleskom jeziku u periodu od početka 2010. godine do juna 2014. godine. **Zaključak.** Kao zaključak ovog sistematičnog pregleda o efikasnosti metoda za indukciju ovulacije, koji potvrđuje i dopunjuje prethodna saznanja iz ove oblasti, može se formirati terapijski algoritam za indukciju ovulacije kod pacijentkinja sa sindromom policističnih jajnika, koji čine sledeći koraci: 1) modifikacija životnog stila; 2) indukcija ovulacije klomifen-citratom; 3) primena metformina; 4) upotreba inhibitora aromataze; 5) primena gonadotropina i laparoskopjska punkcija jajnika – kao druga terapijska linija i 6) asistiranje reproduktivne tehnike.

Ključne reči: Indukcija ovulacije; Sindrom policističnih jajnika; Algoritmi; Ishod lečenja; Anovulatorni ciklus; Infertilitet žene; Životni stil; Klomifen; Metformin; Inhibitori aromataze; Gonadotropini; Laparoskopija; Asistirane reproduktivne tehnike

resistance, hyperinsulinemia) are often associated with this disorder, but it is not yet clear if they are part of the disease or comorbidities [3]. PCOS amounts to 16.6% according to the results of the most recently published study, which is at the same time the most comprehensive study of PCOS prevalence based on the widely accepted criteria of the Rotter-

Abbreviations

PCOS – polycystic ovary syndrome
 BMI – body mass index

dam consensus 2003. The therapeutic approaches differ in dependence of whether the reproductive problems are of primary concern, since PCOS is the most frequent cause of anovulatory infertility, or there are some other PCOS consequences. In view of the fact that ovulation and pregnancy in patients with PCOS can be a result of some less aggressive and more economic therapeutic methods, the treatment assumes a gradual approach – from simple noninvasive to expensive and demanding procedures.

The therapeutic modalities for ovulation induction mentioned in the literature are: body mass reduction, use of metformin, clomiphene citrate, aromatase inhibitors, gonadotropins, and surgical techniques of ovulation induction – wedge resection of ovaries, which is abandoned in modern times, and laparoscopic ovarian drilling [4–9].

Starting from the data obtained by the systematic survey of the literature concerning particular ovulation induction methods in respect of the reproductive outcome, the aim of this paper was to establish an algorithm for the induction of ovulation, to treat the infertility in patients with PCOS.

Material and Methods

A detailed search of the literature was carried out in September of 2014 using the PubMed and Scopus electronic databases. The keywords were: '*lifestyle modification*' OR '*clomiphene citrate*' or '*letrozole*' or '*metformin*' or '*gonadotrophins*' or '*IVF*' and '*PCOS*' and '*induction ovulation*' and '*ovulation*' and '*pregnancy*'. The search was limited to clinical investigations carried out on human subjects, published in English in the period from the beginning of 2010 to June 2014.

The search was made of the corresponding abstracts with the aim of identifying the papers relevant to the subject of the study. Full texts of all the pertinent studies accessible via the Academic Network of Serbia and via the Serbian Library Consortium for Coordinated Acquisition (KoBSON) were collected and analyzed.

The criteria for inclusion into the systematic literature search were: 1) study of the type of a randomized controlled study and 2) reproductive outcome (rate of ovulation or pregnancy) as a measure of the effect of a given therapeutic procedure. The selection excluded the studies concerning systematic surveys and/or meta-analyses, as well as review articles.

Data extraction – From each selected study the following data were extracted: author(s) name(s), number of subjects included in the study, interventions performed, estimated outcome, results, and conclusion.

Results

Out of 72 studies identified in this research, 54 were found via the PubMed and 18 via the Scopus database. One study was excluded as a duplicate,

and 27 studies were concluded not to be related to the research subject. Since the full text was not available for 12 studies, they also had to be excluded. After searching the abstracts of the remaining studies, 7 were excluded because of the lack of data about the outcome of interest, and 14 were the articles of a systematic review type, meta-analyses, and review articles. Finally, 11 studies remained to be included in this survey, and they were meticulously studied to draw the required data.

The samples of all studies included women with PCOS and chronic anovulation. The estimated outcomes of interest were the ovulation rate (OR) and/or pregnancy rate (PR), and, where it was available, the live birth rate was also taken into account. The results and conclusions of the studies are given in **Table 1**.

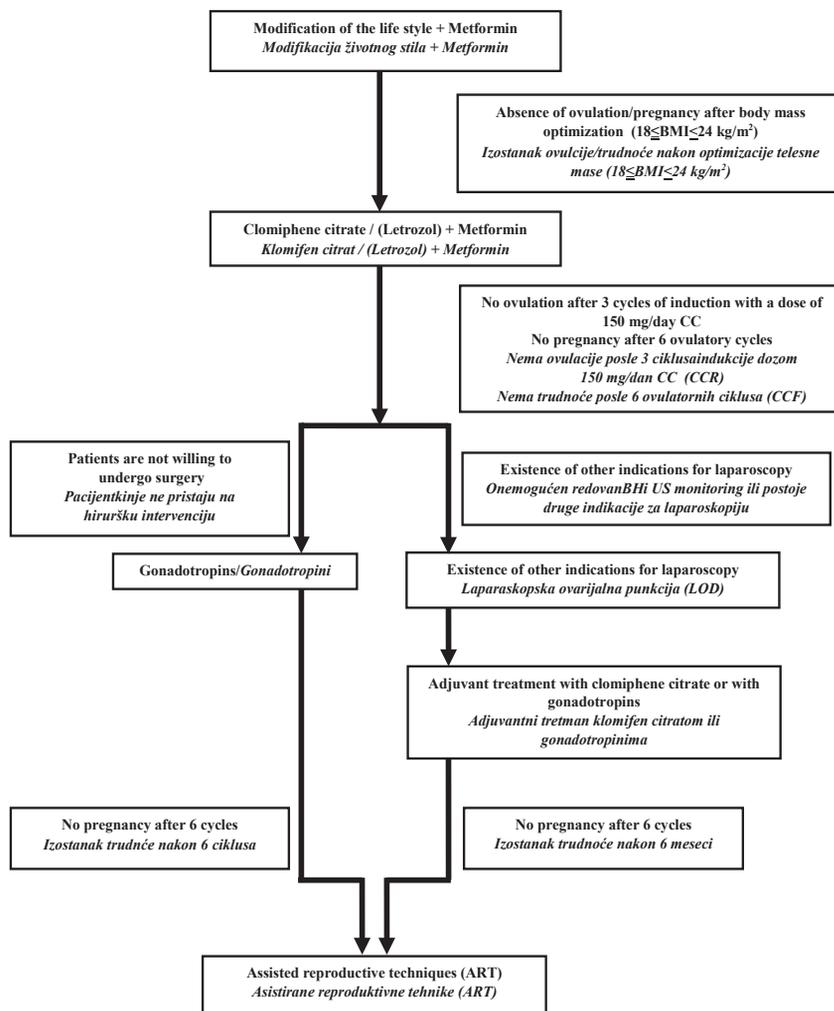
Discussion

The body mass index (BMI) is known to be in opposite correlation with the response to some drugs that are used in the ovulation induction, and the modification of life style and decrease in the body weight improve the response to the ovulation inductors and contribute to a better reproductive outcome [10–12]. Such an attitude was also confirmed by the results of a study encompassed by this survey [13]. The study of Morin-Papunen et al. showed the statistical significance of the correlation between a three-month pretreatment with metformin and better reproductive outcome, which was especially pronounced in obese patients [14]. Having compared the efficiency of clomiphene citrate and metformin, Baran et al. arrived at the conclusion that ovulation was more frequent in those patients who received clomiphene citrate, although the difference was not statistically significant. Therefore, they have recommended clomiphene citrate as the first line treatment [15]. A similar conclusion was also reached by Homburg et al. [16]. Although the results regarding the reproductive outcome are in favor of the application of gonadotropins, taking into account the overall costs and treatment conformity, the conclusion of this study is that clomiphene citrate should still be considered as the first choice treatment. If ovulation failed to occur after three cycles of induction with clomiphene citrate at a dose of 150 mg/day, such patients are considered to be resistant to clomiphene citrate. Abu Hashim et al., Begum et al. and Abd Elgafor et al. have concluded that the application of metformin in combination with standard ovulation inductors contributes to a better reproductive outcome [17–19]. This finding verifies the recommendations of a number of literature sources proposing that the next step in clomiphene citrate-resistant patients should be the introduction of metformin in therapy since it results in a significantly improved response to clomiphene citrate. This is especially important in case of the patients with BMI > 25 kg/m² and insulin resistance [1]. The results of earlier investigations showed that aromatase inhibitors (i.e. letrozole) ap-

Table 1. Efficiency of ovulation induction methods in patients with PCOS: characteristics of the encompassed studies
Tabela 1. Efikasnost metoda indukcije ovulacije kod pacijentkinja sa PCOS: karakteristike uključenih studija

Author Autor	N	Intervention Intervencija	Assessment Procena	Results/Rezultat	Conclusion/Zaključak
Begum et al. (2013)	165	Pretreatment with M 1500 mg/day 4 weeks A: M + CC (150 mg/day, 5 days) Pretretman M 1500 mg/dan 4 nedelje A: M + CC (150 mg/dan, 5 dana) B: M + rFSH3 (75 IU) C: rFSH (75 IU)	OR PR	OR A: 27.27% B: 89.09% C: 74.55% PR A: 12.73% B: 54.55% C: 29.09%	Metformin enhances the response to the ovulation inductors and is safe for the application in the case of PCOS/Metformin povećava odgovor na induktore ovulacije i bezbedan je za upotrebu u PCOS
Abd Elgafor (2013)	146	A: M (1700 mg/day) + L (5 mg/day, 5 days), B: LOD/A: M (1700 mg/dan) + L (5 mg/dan, 5 dana), B: LOD	OR PR	NS!	Both treatments (M+L and LOD) were equally efficient as second line treatment in CCR patients/Oba tretmana (M+L i LOD) su podjednako efikasna kao tretman 2. linije kod CCR pacijentkinja
Morin Papunen et al. (2012)	320	A: M obese 1500 mg/day; normal body mass – 1000 mg/day) B: placebo A: M gojazne 1500mg/dan; normalna telesna masa - 1000 mg/dan), B: placebo	PR LBR	PR A: 53.6% B: 40.6% LBR A: 41.9% B: 28.8%	Metformin improved the reproductive outcome significantly, especially in obese women, when applied as a three-month pretreatment or in combination with routine means for ovulation induction/Metformin značajno poboljšava reproduktivni ishod posebno kod gojaznih žena primenjen kao tromesečni pretretman ili u kombinaciji sa rutinskim sredstvima za indukciju ovulacije
Homburg et al. (2012)	302	A: CC (50-150 mg/day, 5 days) B: rFSH (50IU) A: CC (50-150 mg/dan, 5 dana) B: rFSH (50IU)	PR LBR	PR A: 41.2% B: 52.1% LBR A: 36.9% B: 47.4 %	Because of the comfort and price, it is recommended that CC should be first line treatment, although low doses of FSH showed better results. Low dose FSH may be first line treatment in older patients./Zbog komfora i cene preporučuje se da CC bude tretman 1. linije, iako niske doze FSH pokazuje bolji rezultat. Niske doze FSH može biti tretman 1. linije kod starijih pacijentkinja.
Banerjee Ray (2012)	147	A: CC 100 mg/day, 5 days B: L 2.5 mg/day, 5 days A: CC 100 mg/dan, 5 dana B: L 2,5 mg /dan, 5 dana	OR PR	OR A: 61.5% B: 86.9% PR A: 17.9% B: 28.9%	L is safe and equally efficient as CC when ovulation is concerned. In contrast to CC, L has a positive effect on the endometrium, potentially increasing the probability of pregnancy after the successful induction of ovulation./L je bezbedan i podjednako efikasan kao i CC u postizanju ovulacije. Za razliku od CC, L ima pozitivan efekat na endometrijum, čime se potencijalno povećava verovatnoća trudnoće nakon uspešne indukcije ovulacije.
Ramezan Zadeh et al.	67	A: L 5 mg/day B: L 7,5 mg/day A: L 5 mg/dan B: L 7,5 mg/dan	OR PR	OR A: 90% B: 89.2% PR A: 25.8% B: 21.2% NS !	A 7.5 mg/day dose of L is not advantageous over a 5 mg/day dose of L as first line treatment. A higher dose of L is not advantageous in respect of the thickness of the endometrium. Doza L od 7,5mg/dan ne predstavlja prednost u odnosu na dozu 5 mg/dan L kao tretmana prve linije. Veća doza letrozola nema prednosti ni u pogledu debljine endometrijuma.
Abu Hashim et al. (2011)	282	A: M (1500 mg/day) + CC (50-150 mg/day) B: LOD A: M (1500 mg/dan) + B: LOD	OR PR	OR A: 67.0% B: 68.2% PR A: 15.4% B: 17.0% * all patients with BMI< (24.8+/-1.7) achieved ovulation in the M-CC treatment/* sve pacijentkinje sa manjim BMI (24,8+/-1,7) postigle su ovulaciju M-CC tretmanom	The M-CC combination is equally efficient in achieving ovulation and pregnancy as LOD in CC-resistant patients during six months. It is recommended that the CC-M treatment should be preferable in younger patients. For patients over 35, the recommendation is the induction with gonadotropins or IVF. All obese patients need to optimize their body mass. Kombinacija M-CC je podjednako efikasna u postizanju ovulacije i trudnoće kao i LOD kod CC rezistentnih pacijentkinja tokom 6 meseci praćenja. Predlaže se da se tretmanu CC-M da prednost kod mladih pacijentkinja. Za pacijentkinje iznad 35 god. predlaže se indukcija gonadotropinima ili IVF. Sve gojazne pacijentkinje trebale bi da optimizuju telesnu masu.
Palomba et al. (2010)	96	A: 6-week physical activity + diet (1000 kcal/day) B: CC (150 mg/day) C: physical activity + diet + CC (150 mg/day) A: 6 nedelja fizičke aktivnosti + dijeta (1000 kcal/dan) B: CC (150 mg/dan) C: fizička aktivnost + dijeta + CC (150 mg/dan)	OR	OR – statistically significantly higher ovulation rate in the group C (37.5%) vs. group A (12.5%) and B (9.4%) OR – statistički značajno viša stopa ovulacije u grupi C (37.5%) u odnosu na grupu A (12.5%) i B (9.4%)	Six weeks of physical activity + hypocaloric diet increase the probability of ovulation induced with CC in the CCR overweight or obese patients. 6 nedelja fizičke aktivnosti + hipokalorijska dijeta tretmana, povećava verovatnoću ovulacije indukovane CC kod CCR pacijentkinja sa prekomernom telesnom težinom ili gojaznih.
Abu Hashim et al. (2010)	260	A: L 2,5 mg/day d3-7 B: LOD (6 months) A: L 2,5 mg/dan d3-7 B: LOD (6 meseci praćenja)	OR PR LBR	OR: NS A: 65.4% B: 69.3% PR: A: 15.6% B: 17.5%	L and LOD are equally efficient in the induction of ovulation and achievement of pregnancy in CCR patients, but in view of the lower inaviveness and treatment costs, L should be advantageous over LOD./L i LOD su podjednako efikasni u indukciji ovulacije i postizanju trudnoće kod CCR pacijentkinja, ali obzirom na manju invazivnost i cenu tretmana, L bi trebalo da ima prednost nad LOD.
Baran et al. (2010)	69	A: M1700 mg/day B: CC 50-150 mg/day A: M1700 mg/dan B: CC 50-150 mg/dan	OR PR	OR: A:32.3 % B: 60.6% PR: NS A:36.6 % B:35.4%,	CC and M as first line drugs enhanced the pregnancy rate; CC gave better results in achieving ovulation./CC i M kao medikamenti 1. linije povećavaju stopu trudnoća. CC daje bolje rezultate u postizanju ovulacije.
Nejad et al. (2011)	366	IVF	PR	PR: NS	The outcomes of IVF with PCOS patients and patients with tubal infertility are similar./Ishod IVF kod PCOS pacijentkinja i pacijentkinja sa tubarnim infertilitetom je sličan.

Legend: M – metformin, CC – clomiphene citrate, rFSH – recombinant follicle-stimulating hormone, L – letrozole, LOD – laparoscopic ovarian drilling, IVF – in vitro fertilization, NS – not statistically significant, OR – ovulation rate, PR – pregnancy rate, LBR – live birth rate
 Legenda: M= metformin, CC= kломifen citrat, rFSH= rekombinantni folikulo-stimulirajući hormon, L= letrozol, LOD= laparoskopjska punkcija jajnika, IVF= in vitro fertilizacija, NS= nije statistički značajno, OR – stopa ovulacije, PR – stopa trudnoće, LBR – stopa živorođene dece, PCOS – sindrom policističnih jajnika



Scheme 1. Treatment algorithm for the ovulation induction in PCOS patients

Schema 1. Terapijski algoritam indukcije ovulacije kod pacijentkinja sa sindromom policističnih jajnika

peared to be another candidate for the first choice drug [20]. A main advantage of letrozole over clomiphene citrate is its positive effect on the endometrium. This was confirmed by the study of Banerjee Ray et al. [21]. Ramenzanzadeh et al. found that there was no significant difference in the reproductive outcome when higher daily doses of letrozole were administered [22]. In view of the advantages of letrozole over clomiphene citrate, this drug could be also an adequate option for second choice treatment in clomiphene citrate-resistant patients. Two studies from this survey confirmed that letrozole, that is the combination of letrozole and metformin, were as efficient as laparoscopic ovarian drilling [17, 19]. This survey did not identify any study which had investigated potential teratogenicity of letrozole, and this is, according to some earlier results, one of the main reasons that can limit the use of letrozole in the treatment of ovulatory infertility.

When the reproductive outcome is concerned, the advantage of the application of gonadotropins over

clomiphene citrate was also confirmed by the results of this literature search. Begum et al. found that the percentage of ovulatory cycles and achieved pregnancies were statistically significantly higher in the treatments with gonadotropins compared to the combination of clomiphene citrate + metformin [18]. The same study showed that the addition of metformin improved the effect of recombinant follicle-stimulating hormone. A similar result has also been obtained by Homburg et al. pointing out that the high price of gonadotropins is the main reason why they are not a reserve treatment option, that is the first option in older patients [16].

Laparoscopic ovarian drilling is another option to be taken into account in case of clomiphene citrate-resistant patients. The studies encompassed by this survey show that there is no statistically significant difference in the rate of ovulation/pregnancy when laparoscopic ovarian drilling is compared to medicamentous treatments – clomiphene citrate + metformin, letrozole alone or letrozole + metformin [17, 19, 23]. Since this is still an invasive

procedure with potential postoperative complications, the recommendation of the studies encompassed by this survey and of some other literature sources is that laparoscopic ovarian drilling should be considered as a second treatment line in the patients that have also some other indications for laparoscopy [9, 17].

If none of the above methods gives desired results, that is when the infertility causes persist, some of the assisted reproductive techniques remain as the last treatment option. Nejad et al. showed that the reproductive outcome of *in vitro* fertilization in PCOS patients is not statistically significantly different compared to that observed in patients with tubal infertility [24], which is also in line with the results of some other studies [25] and meta-analysis [26].

Conclusion

Based on the conclusion that can be drawn from this systematic survey of the methods concerning ovulation induction, which confirms and supplements the previous knowledge in the field, it is possible to form an algorithm for induction of ovulation in patients with polycystic ovary syndrome, which consists of the following steps: 1) modification of the life style accompanied by potential adjuvant therapy with metformin, aimed at optimizing the body mass and solving the

problem of insulin resistance, should be the first treatment step for women with body mass index $>30 \text{ kg/m}^2$, which can directly lead to ovulation or contribute to a better effect of the procedures applied in the further treatment; 2) induction of ovulation with clomiphene citrate as a standard first pharmacological line for patients having polycystic ovary syndrome; 3) application of metformin in combination with clomiphene citrate – which increases the chances of ovulation and gestation so that this combination can be applied from the beginning of the treatment or in case of clomiphene citrate-resistant patients; 4) application of aromatase inhibitors which can substitute clomiphene citrate as the first line treatment, but the proofs of the superiority of letrozole over clomiphene citrate are still insufficiently strong, whereas its application is additionally compromised by its potential teratogenicity; 5) application of gonadotropins and laparoscopic ovarian drilling, which represent the second treatment line; 6. assisted reproductive techniques is the last treatment option if pregnancy does not occur even after six cycles of induction with gonadotropins, that is after six months from the laparoscopic ovarian drilling, or when there are some associated causes of infertility.

The algorithm for induction of ovulation in patients with polycystic ovary syndrome is illustrated in **Scheme 1**.

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