Gineco.eu [13] 42-45 [2017]
DOI: 10.18643/gieu.2017.42

Controversies in polycystic ovarian syndrome

I. Popescu[1], C. Ionescu[1,2], M. Dimitriu[1,2], R. Bohîlțea[2,3], R. Viezuină[1], B. Davitoiu[1], I. Pacu[1,2]

1. Department of Obstetrics and Gynecology "St. Pantelimon" Clinical Emergency Hospital, Bucharest, Romania
2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
3. Department of Obstetrics and Gynecology University Emergency Hospital, Bucharest, Romania

Correspondence: Dr. Cringu Ionescu e-mail: antoniuginec@yahoo.com

Abstract

Polycystic ovarian syndrome (PCOS) is a fairly frequent syndrome but yet a subject that meets a lot of controversies. We believe that all controversies surrounding PCOS are due to its heterogeneity and complexity but also to its uncertain etiology. This review is based on the results of clinical trials and studies published until present. Our aim is to present the evolution of the perspective on the subject and the controversies still surrounding it. Considering the diagnosis, the majority of medical community uses the Rotterdam criteria, and Androgen Excess Society considers PCOS a „disorder of androgen excess or hyperandrogenism" thus including hyperandrogenism as a compulsory criterion in its diagnosis. A number of theories and hypothesis have been launched over the years regarding the etiology of PCOS, none of them being flawless or able to explain the entire panel of symptoms. Treatment of PCOS does not address the cause itself but rather focuses on its effects: either anovulation, oligomenorrhea, effects of hyperandrogenism and metabolic changes. The existing guidelines are still not specific enough, while personal experience plays a major role in the medical conduct leading to many controversies. As a result, every PCOS guideline is rather a consensus than a nondisputable fact. Considering nowadays, there is a persistent need for more and greater studies researching new ideas, new genes, and new therapies.
Keywords: *polycystic ovarian syndrome, oligomenorrhea, hyperandrogenemia*

Introduction

Polycystic ovarian syndrome (PCOS) is a fairly frequent syndrome but yet a subject that meets a lot of questiona. It was first described by Stein and Leventhal in 1935 and until nowadays we have come to understand this pathology on a different level, still, after more than 80 years, there are yet a lot of controversies surrounding this subject. We believe that all controversies surrounding PCOS are due to its heterogeneity and complexity but also to its uncertain etiology[(1)].

This review is based on the results of clinical trials and studies published in journals from the moment it was first acknowledged. Our aim is to present the evolution of the perspective on the subject and the controversies still surrounding it.

Controversies in diagnosis

In the years following the establishment of National Institute of Child Health and Human Development criteria since 1990 it became obvious that basing on diagnosis, was insufficient due to the fact that they were established without any data from clinical trials but rather based on the opinion of the specialists tasked with their development[(2)]. These criteria included: i) chronic anovulation with ii) clinical and/or biochemical hyperandrogenism with exclusion of other etiologies of androgen excess and anovulatory infertility but without any reference about the polycystic ovaries found on ultrasound[(2)]. As a response to this issue, the 2003 consensus established the Rotterdam criteria. Therefore, in order to diagnose PCOS one has to meet two of the following three criteria: i) oligo- or chronic anovulation, ii) clinical and/or biochemical signs of hyperandrogenism and/or iii) polycystic ovaries with the same specification as earlier regarding the exclusion of other androgen excess and anovulatory infertility etiologies[(1)]. Even though the revised criteria added the ultrasonographic aspect of the ovaries, following them implies that PCOS may be diagnosed without any signs of hyperandrogenism, either clinical or biochemical. While gynecologists follow the 2003 Rotterdam criteria, endocrinologists do not take lightly the matter, therefore the need for another set of criteria. A principal conclusion of the task force put in place by Androgen Excess Society (AES) in 2006 was that PCOS should be, first of all, considered a „disorder of androgen excess or hyperandrogenism", at the same time nothing that „a minority considered the possibility that there may be forms of PCOS without any evidence of hyperandrogenism"[(3)]. To summarize, the 2006 AES guidelines state that in order to diagnose PCOS the following two criteria are necessary: i) hirsutism and/or hyperandrogenemia, and ii) oligo-anovulation and/or polycystic ovaries after the exclusion of other etiologies of anovulatory infertility and androgen excess[(3)].

Acknowledge the heterogeneity of the syndrome, four clinical phenotypes are usually found[(4)]:

- Phenotype A (i.e. classic PCOS) including polycystic ovaries, hyperandrogenism and oligo-anovulation,
- Phenotype B (i.e. hyperandrogenic anovulation) including hyperandrogenism with oligo-anovulation
- Phenotype C (i.e. ovulatory PCOS) including polycystic ovaries (e.g. without ovulatory dysfunction) and hyperandrogenism,
- Phenotype D (i.e. non-hyperandrogenic PCOS) including polycystic ovaries and oligo-anovulation[(4)].

Not only the presence of hyperandrogenemia falls into debate but also the biochemical criteria were needed in

Received: *January 06, 2017*
Revised: *January 20, 2017*
Accepted: *February 22, 2017*

order to make the diagnosis. First of all, there is no unanimous consensus on the matter of the normal androgen levels neither in women nor the androgens which should be measured in order to diagnose PCOS[5]. High serum levels of testosterone (i.e. total or free), androstenedione, and dehydroepiandrosterone (DHEA) are classically used in order to define hyperandrogenemia, yet some studies showed that decreased sex hormone-binding globulin (SHBG) levels, and increased free testosterone (i.e. not total testosterone) concentration and DHEA concentrations, are most suggestive for PCOS hyperandrogenemia[6,7]. Moreover, controversies regarding which methods should be used when assessing androgens in women are still exist[6]. The most recent studies bring forward 11-oxygenated androgens which are the most characteristic for the syndrome[8].

Clinical hyperandrogenemia also falls under controversy. Considering the hirsutism, one of the most prominent manifestations of hyperandrogenemia, we may avoid subjectivity using the Ferriman-Gallwey score[9]. Alopecia, while considered until recently as a sign of virilization, is not that frequent in cases of women with PCOS[10]. Although there are scales for establishing hair loss in women, they are rarely used in clinical practice. Acne also is can be seen frequent in women with PCOS[3], particularly in young women. Therefore, it is unclear whether the prevalence of acne is higher in women with PCOS compared with the rest of the population as there are no reliable clinical trials on these subjects[11].

Oligomenorrhea, frequently a consequence of anovulation, is defined as "menstrual cycles at more than 35 days interval"[6]. We need to specify the fact that ovulatory dysfunction, an important criterion for diagnosing the PCOS, is not necessarily associated with menstrual irregularity[12].

Polycystic ovaries are usually defined by Rotterdam criteria based on total follicle number (e.g. the presence of 12 or more follicles throughout the ovary measuring from 2 to 9 mm in diameter) or on increased ovarian volume (i.e. more than 10 cm^3)[1]. Until present, studies showed that more than 50% of healthy women have more than 12 follicles per ovary[13], this being the main reason why specialist often prefer to consider a polycystic ovary when the number of follicles exceeds 20/ovary[14].

Controversies in etiology

A number of theories and hypothesis have been launched over the years regarding the etiology of PCOS. In 1980-1990's a series of theories have emerged related to the origin of PCOS though each of them seemed relevant, but none founded to be the main cause of PCOS.

Intrauterine theory stipulated that exposure to androgens during intrauterine life or neonatal period would alter fetal ovaries[15] or can lead to congenital masculinization of hypothalamus[16] thus explaining PCOS hyperandrogenemia while reduced pancreas growth *in utero*[17].

Other studies considered that various mechanisms during childhood and puberty should be blamed for the syndrome. For example Insulin-Like Growth Factor 1 (IGF1), whose' levels are increased in infancy after periods of protein excess, is believe to influence ovarian steroidogenesis[18]. Both Mechanick and Insler suggest that PCOS finds its origins during the puberty. While the first believes that it's due to abnormal brain development as a result to aberrant puberty[19] the second suggests that PCOS hyperandrogenemia is the result of increased adrenal production during puberty[20].

Other studies shows that intra-ovarian factors are considered for the majority of the PCOS manifestations. First of all, Puzigaca et al. stipulates that enlarged ovaries found in PCOS women are related to excessive androgen production[21]. Interestingly, studies showed that ovarian secretion of IGFs is the possible cause of increased insulin resistance and adrenal androgen secretion[22,23].

The genetic theory known from 1970's, underwent complex changes. The thory concluded the idea that PCOS was transmitted in X-linked dominant fashion[24], a hypothesis infirmed years ago, but which opened new ways of studies confirming the role of heritability in PCOS. Some studies showed that up to 80.5% of women sibling of PCOS women are affected[25] attesting the genetic origin of PCOS and infirming in the same time both autosomal dominant or X-linked dominant modes of inheritance. The complexity of the syndrome, overall, upholds the idea of its polygenic origin[26], recent studies showing that general transcription factor IIA subunit 1 like and luteinizing hormone/choriogonadotropin receptor may serve as biomarkers[27] while others consider that thyroid adenoma-associated protein gene polymorphism and DENN domain-containing protein 1A gene are involved[28]. The involvement of multiple genes with various effects on the overall disease risk support the theory by which PCOS is an inherited disease[29].

Controversies in treatment

Treatment of PCOS does not address the cause itself but rather focuses on its effects: either anovulation (i.e. for those cases where fertility is desired), oligomenorrhea, effects of hyperandrogenism and metabolic changes. Some studies showed that lifestyle changes are primary therapy in PCOS overweight and obese women for the treatment of metabolic complications[30]. These include reducing body mass index and preventing further weight gain. The main goal is a 5-10% initial weight loss, followed by long term weight loss of 10 to 20% and achieving a waist circumference of less than 88 cm[31]. Therefore, lifestyle changes are the most effective form of treatment for reducing weight, improving insulin sensitivity and decreasing the incidence of metabolic syndrome and type II diabetes, improving in this way risk factors for cardiovascular disease[32,33]. Studies also showed that weight loss has some fertility benefits[34]. Although initial studies researching pharmacological treatment have showed excellent results concerning the weight loss, maintenance of weight loss and reduction of cardiovascular risks[35] some of these drugs were proven to actually increase the risk for cardiovascular events[36] and were removed from

the market[37]. Meanwhile, studies showed that bariatric surgery was associated with improvement or complete resolution of type II diabetes, hypertension, hyperlipidemia and obstructive sleep apnea[38] while others reported complete resolution of all features of PCOS, even hirsutism, hyperandrogenism, anovulation or menstrual irregularity[39,40].

When fertility is desired, the first line measure to induce or restore ovulation (in up to 80% cases of obese women) is considered weight loss[41]. Metformin, an insulin sensitizing drug, is frequently added when a pregnancy is not achieved after weight loss. Insulin sensitizing drugs, from which metformin was the first administrated, were shown to improve menstrual regularity along with reduction of body mass index and androgen levels[42]. Controversies surrounding the usefulness of this drug created the necessity for clinical trials on this subject. Thus, a meta-analysis from 2009, which analyzed the most prominent clinical trials, concluded that metformin indeed leads to significant weight loss compared to placebo but when given to the patients on a diet or on a program of life changes does not contribute majorly[43]. In the same context, studies showed that metformin effectively induces ovulation in PCOS women[44]. Clomiphene citrate is another drug often used to induce ovulation. Research shows that it induces ovulation in 57% of the cases with pregnancy rates higher than 23%[45]. While the association between clomiphene citrate and metformin is frequently encountered, most studies conclude that the association is irrelevant, and the pregnancy rates after clomiphene citrate plus metformin compared to pregnancy rates after clomiphene citrate alone do not differ[46].

Gonadotrophines are often used as second-line treatment, although the original protocol of 150 IU/day is no longer in use due to the increased risk of ovarian hyperstimulation syndrome[47]. Studies showed that in case of PCOS the low-dose protocols are safer, therefore the "step-up" and "step-down" protocols which use 37.5-75IU/day are to be taken into consideration if the patient is unresponsive to the first-line treatment. The medical community prefers the step-down protocol, considering its safety in terms of monofollicular development[48,49]. Although the association between gonadotrophines and gonadotropin-releasing hormone agonists showed to be controversed, some studies have showed a slightly higher rate of pregnancy compared to gonadotrophines alone but also a highr overstimulation rate[47].

Another second-line therapy is represented by laparoscopic ovarian drilling (LOD)[50]. It should be reccommeded in cases characterized by infertility due to anovulation in women with PCOS unresponsive to clomiphene citrate[50]. While there are specialists that consider LOD as efficient as gonadotrophines[50] there are studies that present better pregnancy results for LOD (60%) in comparison to gonadotrophine therapy[51]. Even more, there is still an uncertainty regarding the technic for LOD: while four monopolar or laser punctures have been shown to be effective, and majority uses between four and ten punctures there are some results which shows that a higher number, might lead to premature ovarian failure[50,52]. Neither gonadotrophine therapy nor LOD are risk free: while the first one needs a close monitoring and associates the risk of ovarian hyperstimulation syndrome, LOD associates intraoperative and postoperative risks, especially in overweight women[50].

Anovulation associated with PCOS, alone, is not an indication for *in vitro* fertilization. In case of failure of first-line treatment and when second-line gonadotrophine therapy is considered too risky, *in vitro* fertilization (IVF) is to be taken into consideration[53]. Other cases where IVF has its indications are the patients who besides PCOS associate pathologies such as tubal damage, endometriosis or male infertility[50].

When trying to antagonize only hyperandrogenic features without fertility goals weight loss alone is usually insufficient. Hirsutism and acne, being one of the most prominent and disturbing features in the life of women with PCOS, deserve the full attention of the medical world. Besides the local treatment and mechanical ways for hair removal, in case of mild hyperandrogenic symptoms usually the oral contraceptive pill is efficient. Both severe hirsutism and acne respond to antiandrogens either androgen receptor blockers or 5-alpha-reductase inhibitors (finasteride) often incorporated in oral contraceptives. These could be used as monotherapy or dual therapy along with oral contraceptive pill[54].

In some cases adding metformin to monotherapy or to dual therapy has benefic effects on hyperandrogenisc symptoms due to its effectiveness on lowering testosterone levels and increasing SHGB levels[54]. Only in some special cases of sever hyperandrogenic symptoms refractory to the above treatment, long-acting gonadotropin-releasing hormone analogues along with estrogens may be used although complications of the treatment are equally severe.

Oligoamenorrhea, as a sign of anovulation which associates chronic estrogenization without any progesterone exposure, with its known effects upon the endometrium, is highly treatable. Medical society still searches for new therapies for PCOS. We believe it is important for us to mention the inositols, which although were discovered in 1850's, it found its use in the treatment of PCOS as late as 1993[55]. Therefore, their efficiency in ovarian stimulation and their benefic effect on insulin sensitivity has been clearly showed in women suffering from PCOS both obese and normal weighted[56] along with their capacity of lowering androgen levels[57]. Studies showed that inositols also improve the metabolic profile by lowering total cholesterol level, triglyceride level, glucose and insulin levels[58].

Conclusions

Due to its heterogeneity and complexity this syndrome is surrounded by controversies, not only in the matter of diagnosis and treatment but also its etiology. As a result, every PCOS guideline is rather a consensus than a non-disputable fact. There is a persistent need for more and greater studies researching new ideas, new genes, and new therapies. ■

References

1. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004, 81(1), 19-25.
2. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004, 89(6), 2745-9.
3. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W. et al. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society Guideline. J Clin Endocrinol Metab 2006, 91(11), 4237-45.
4. Johnson TRB, Kaplan LK, Ouyang P, Rizza RA. Evidence-based methodology workshop on polycystic ovary syndrome, 2012. Executive Summary. http://prevention.nih.gov/workshops/2012/pcos/docs/FinalReport.pdf
5. Barth JH, Yasmin E, Balen AH. The diagnosis of polycystic ovary syndrome: the criteria are insufficiently robust for clinical research. Clin Endocrinol (Oxf) 2007, 67(6), 811-5.
6. Botsis D, Kassanos D, Pyrgiotis E, Zourlas PA. Sonographic incidence of polycystic ovaries in a gynecological population. Ultrasound Obstet Gynecol 1995, 6(3), 182-5.
7. Escobar-Morreale HF, Asuncion M, Calvo RM, Sancho J, San Millan JL. Receiver operating characteristic analysis of the performance of basal serum hormone profiles for the diagnosis of polycystic ovary syndrome in epidemiological studies. Eur J Endocrinol 2001, 145(5), 619-24.
8. O'Reilly MW, K empegowda P, Jenkinson C, Taylor AE, Quanson JL, Storbeck KH, Arlt W.11-oxygenated C19 steroids are the predominant androgens in polycystic ovary syndrome. J Clin Endocrinol Metab. 2016 Nov 30, jc20163285.
9. Barth JH, Yasmin E, Balen AH. The diagnosis of polycystic ovary syndrome: the criteria are insufficiently robust for clinical research. Clin Endocrinol (Oxf) 2007, 67(6), 811-5.
10. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol 1977, 97(3), 247-54.
11. Lujan ME, Chizen DR, Pierson RA. Diagnostic Criteria for polycystic ovary syndrome: pitfalls and controversies. J Obstet Gynaecol Can 2008, 30(8), 671-9.
12. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007, 370(9588), 685-97.
13. Diamanti-Kandarakis E, Panidis D. Unravelling the phenotypic map of polycystic ovary syndrome (PCOS): a prospective study of 634 women with PCOS. Clin Endocrinol (Oxf) 2007, 67(5), 735-42.
14. Allemand MC, Tummon IS, Phy JL, Foong SC, Dumesic DA, Session DR. Diagnosis of polycystic ovaries by three-dimensional transvaginal ultrasound. Fertil Steril 2006, 85(1), 214-9.
15. Hague WM. Millar DR. Excessive testosterone secretion in pregnancy. Case report. Br J Obstet Gynecol 1985, 192, 173-8.
16. McCluskey SE, Evans C, Lacey JH, Pearce 1M, Jacobs H. Polycystic ovary syndrome and bulimia. Fertil Steril 1992, 55, 287-91.
17. Phillips K. Barker DJP, Hales CN. Fall CHD, Osmond C, Clark PMS. Fetal growth and impaired glucose tolerance in men and women. Oiabetologia 1993, 36, 225-8.
18. Kazer R. The aetiology of polycystic ovary syndrome (PCO). Med Hypothesis 1989, 30, 151-5.
19. Mechanick II, Futterweit W. Hypothesis: abberant puberty and the Stein-Leventhal syndrome. Int I Fertil 1984, 29, 35-8.
20. Insler V, Lunenfeld B: Pathophysiology of polycystic ovarian disease: new insights. Hum Reprod 1991, 6, 1025-9.
21. Puzigaca Z, Prelevic GM, Stretenoric Z, Balint-Peric L. Ovarian enlargement as a possible marker of androgen activity in polycystic ovary syndrome. Gynecol Endocrinol 1991, 5, 167-74.
22. Hammond JM. Baranao ILS, Skaleris D, Knight AB, Downloaded from mjiri.iums.ac.ir at 20:29 IRST on Saturday February 18th 2017 Polycystic Ovary Syndrome Romanus J A. Matthew MR. Production of insulin-like growth factors hy ovarian granulosa cells. Endocrinol 1985, 117, 2553-5.
23. Kazer R. The aetiology of polycystic ovary syndrome (PCO). Med Hypothesis 1989, 30, 151-5.
24. Givens JR, Andersen RN, Umstot ES, Wiser WL: Clinical findings and hormonal responses in patients with polycystic ovarian disease with normal versus elevated LH levels. Obstet Gynecol 1976, 147, 388-94.
25. Hague WM, Adams J, Reeders ST, Pelo TEA, Jacobs HS: Familial polycystic ovaries: a genetic disease. Clin Endocrinol (Oxf.) 1986, 29, 593-605.
26. Shayester J, John E. Genetic and non-genetic theories on the etiology of Polycystic Ovary Syndrome: A review. From the School o/Obstetrics and Gynaecology, University o/New South Wales, Royal Hospital/or Women, 188 Oxford St., Paddington, 2021 NSW. MIIRI 1997, II(2), 169-75.
27. Thathapudi S, Kodati V, Erukkambattu J, Addepally U, Qurratulain H. Association of luteinizing hormone chorionic gonadotropin receptor gene polymorphism (rs2293275) with polycystic ovarian syndrome. Genet Test Mol Biomarkers 2015, 19(3), 128-32.
28. Brower MA, Jones MR, Rotter JI, Krauss RM, Legro RS, Azziz R, Goodarzi MO. Further investigation in europeans of susceptibility variants for polycystic ovary syndrome discovered in genome-wide association studies of Chinese individuals. J Clin Endocrinol Metab 2015, 100(1), E182-6.
29. Goodarzi MO. Looking for polycystic ovary syndrome genes: rational and best strategy. Semin Reprod Med 2008, 26, 5-13.
30. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009, 92(6), 1966-82. doi: 10.1016/j.fertnstert.2008.09.018.
31. National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in adults. Canberra: Australian Government Publishing Service, 2003.
32. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002, 346, 393-403.
33. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S. et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 2005, 142, 611-9.
34. Ayyad C, Andersen T. Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obes Rev 2000, 1, 113-9.
35. Rubio MA, Gargallo M, Isabel Millan A, Moreno B. Drugs in the treatment of obesity: sibutramine, orlistat and rimonabant. Public Health Nutr 2007, 10, 1200-5.
36. Legro RS, Obesity and PCOS: Implications for Diagnosis and Treatment. Semin Reprod Med 2012, 30(6), 496-506. doi: 10.1055/s-0032-1328878.
37. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, Hilton L, Suttorp M, Solomon V, Shekelle PG, Morton SC. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med 2005, 142(7), 532-46.
38. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004, 292, 1724-37.
39. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millan JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2005, 90, 64-9.
40. Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G. et al. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surg Obes Relat Dis 2005, 1, 77-80.
41. Moran LJ, Brinkorth G, Noakes M. et al. Effects of lifestyle modification in polycystic ovarian syndrome. Reprod Biomed Online 2006, 12, 569-78.
42. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy.Metabolism 1994, 43(5), 647-54.
43. Nieuwenhuis-Ruifrok AE, Kuchenbecker WK, Hoek A, Middleton P, Norman RJ. Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis.Hum Reprod Update 2009, 15(1), 57-68.
44. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev 2003, (3), CD003053.
45. Patel H, Patel P, Dikshit RK, Shah S. The efficacy and safety of clomiphene citrate and metformin on ovulation induction in patients suffering from anovulatory infertility.IJBCP 2015, 4(6), 1241-6. doi: 10.18203/2319-2003.ijbcp20151366 Research Article
46. Palomba S, Pasquali R, Orio FJr, Nestler JE. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. Clin Endocrinol (Oxf). 2009, 70(2), 311-21.
47. Nugent D, Vanderkerchove P, Hughes E. et al. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2000, (3), CD000410.
48. Christin-Maitre S, Hugues JN. A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome. Hum Reprod 2003, 18, 1626-31.
49. van Santbrink EJ, Eijkemans MJ, Laven JS, Fauser BC. Patient-tailored conventional ovulation induction algorithms in anovulatory infertility. Trends Endocrinol Metab 2005, 16, 381-9.
50. The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod 2008, 23(3), 462-77. https://doi.org/10.1093/humrep/dem426.
51. Arain F, Arif N, Halepota H. Frequency and outcome of treatment in polycystic ovaries related infertility. Pak J Med Sci 2015, 31(3), 694-9. doi: 10.12669/pjms.313.8003.
52. Malkawi HY, Qublan HS, Hamaideh AH. Medical vs. surgical treatment for clomiphene citrate-resistant women with polycystic ovary syndrome. J Obstet Gynaecol 2003, 23, 289-93.
53. van Santbrink EJ, Fauser BC. Is there a future for ovulation induction in the current era of assisted reproduction? Hum Reprod 2003, 18, 2499-502.
54. Barba M, Schunemann HJ, Sperati F. et al. The effect of metformin on endogenous androgens and SHBG in women: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2009, 70, 661-70.
55. Larner J. D-chiro-inositol–its functional role in insulin action and its deficit in insulin resistance. Int J Exp Diabetes Res 2002, 3, 47-60.
56. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiroinositol in the polycystic ovary syndrome. N Engl J Med 1999, 340, 1314-20.
57. Genazzani AD, Lanzoni C, Ricchieril F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol 2008, 24, 139-44.
58. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. European Review for Medical and Pharmacological Sciences 2009, 13, 105-10.