Reproductive disorders in patients with Metabolic Syndrome and Obesity: Pathogenesis, Clinical Manifestations and Prevention

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Abstract. The issues of pathogenesis, clinical manifestations, outcomes and prevention of reproductive disorders and infertility in patients with metabolic syndrome (MetS) and obesity studied. It was found that the main reproductive disorders of men with MetS were decreased testosterone levels, decreased sperm fertility and erectile dysfunction. In women with MetS, metabolic disorders also lead to reproductive disorders such as infertility, menstrual irregularities, premature birth, births of children with congenital anomalies. Reproductive disorders in patients with MetS can have negative consequences for individuals as reduced quality of life, depression and increasing metabolic disorders, and for the countries as depopulation. Normalization of basal metabolic rate by exercise and a diet improves reproductive health in patients with MetS. However, despite the proven positive impact of lifestyle adjustment, the search for the best cures' treatment for reproductive disorders of patients with MetS remains open.

Keywords: metabolic syndrome, infertility, reproductive health, lifestyle

Introduction. The metabolic syndrome (MetS) increase prevalence leads to growing attention of medical specialists to the study of pathogenesis and consequences of this disease [1]. A study of The influence of lifestyle modifying on the MetS is studied, also MetS pathogenesis and improving treatment schemes are investigated.

It is proved that lifestyle modification is an effective factor in combating the development of cardiovascular, mental and other events as a result of the metabolic disorders, the attention of researchers is primarily aimed at these questions [1-2]. Associated with the MetS infertility, reproductive losses and birth of children with congenital pathology are less studied. Although these conditions are not lifethreatening they may have such serious consequences as a life quality decrease, depression, strengthening MetS for individuals and depopulation for the country's population. The urgency of the study of the influence of metabolic disorders in the human body on its

reproductive health is also due to the fact that in various populations near 20-40% of the population of reproductive age has MetS [1].

The purpose of publication is to light the basic reasons for the development of reproductive health in patients with metabolic syndrome and lifestyle role in the prevention of negative reproductive events.

Research methods. For the analysis of modern ideas about the pathogenesis of reproductive health in patients with Mets, a search for Coochrane Library, Medline, WHO recommendations and leading European and American associations on management of patients with Mets, infertility and other reproductive disorders are studied.

The Results

Reproductive Function

Reproductive function providing is an urgent problem for health care system and society [3]. The social significance of reproductive health preservation is concerned with fertility rates decrease in the European region, the United States, Japan, Hong Kong [4]. The reproductive system provides normal ovogenesis, spermogenesis, pregnancy, baby paste and birth. Necessary conditions for this is the initiation of the processes of ovogenesis and spermogenesis by secretion of Gonadotropin-Releasing Hormone (GNRH) [5], a satisfactory blood supply to all organs and systems, Mental Health, as well as a number of cascading metabolic reactions carried out by such hormones such as Leptin, Insulin and Greelin [6-7]. Violations at any stage of this process lead to significant and, sometimes, irreversible consequences [8-9]. Reproductive health is also assosiated with the general and sexual health [10].

Most of reproductive disorders and infertility are caused be endocrine, metabolic factors and occur as a result of long-term inflammation [11]. The exact data on the spread of infertility and reproductive disorders can not be obtained, since the presence of such violations is detected only when appealing to a doctor, but according to [12], infertility has 8-12% of reproductive age couples. The statistical data show that, although it is more likely to be feminine infertility, the proportion of the male factor is a leading or very important (not less than 40-50%) [12]. But, as a rule, the prevalence of male infertility in the population is much lower than real indicators. In Ukraine there

is a tendency of the female and male infertility prevalence increase (Fig.1), and the infertile couples fraction is about 10-15%. According to the Ministry of Health data, the ratio between women and men is determined today as 3.5: 1, while 20 years ago the ratio between women and men was determined as 8.2: 1.

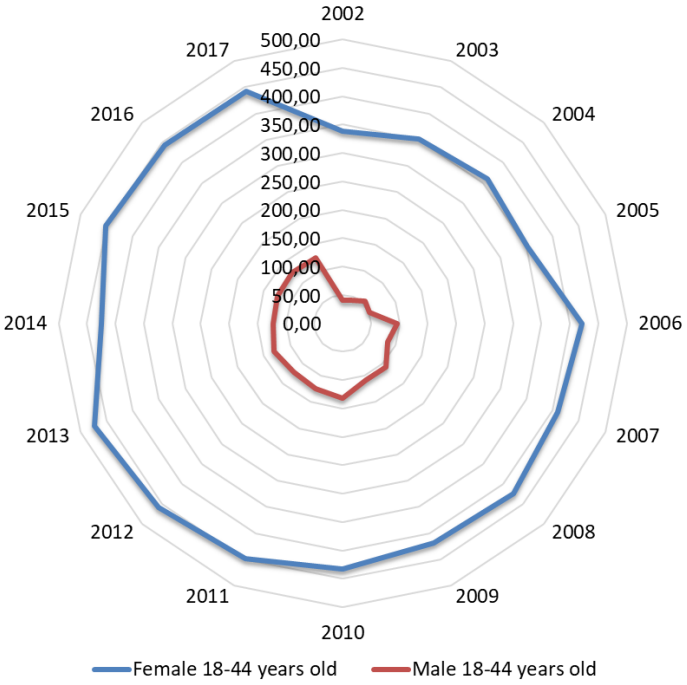

Figure 1. The prevalence rate of infertility per 100000 in Ukraine (data of the Ministry of Health of Ukraine)

The connection between MetS and reproductive disorders and infertility [13] have been proved. Studies show that one of eight Europeans who are drawn to a doctor about infertility, has MetS [14]. Meta-analysis data [15] also demonstrate a decrease in male fertility in patients with MetS and recommend further research in this direction. Metabolic syndrome appears in a third of infertile women with Polycysticovary Syndrome [16]. Also, research demonstrate decreased reproductive health in obesity patients [17]. As more and more adults [18], children and adolescents [19] are suffering from obesity, it is important to provide scientific search towards the prevention of reproductive disorders, infertility and obesity.

These trends initiated a number of multidisciplinary studies of reproductive function in such metabolic disorders as obesity, insulin resistance and diabetes mellitus [20-24]. A study of expression and induction of Hypothalamic-Pituitary-Gonadal (HPG) Axis, GnRH [25-26] genes are promising researches in this feild.

Well-known and studied issues are the influence of professional harm, ionizing radiation, infectious diseases, some medicines and harmful habits and scientific research in this direction continues [27-29]. The harmful environmental factors affect not only the reproductive system, but also the other endocrinological functions. The influence of stress factors on the reproductive function [30] is investigated. Investigations devoted to the reproductive health preservation of the oncological patients are performed [31].

Extremely relevant issues are to find ways to prevent reproductive and metabolic disorders and to form a habit of a healthy lifestyle. The research in this direction will be presented below.

Pathogenesis and clinical manifestation of reproductive disorders in patients with metabolic syndrome / obesity

The main reasons for the violation of reproductive function in both men and women with Mets are an oxidative stress caused by dyslipidemia, insulin resistance, leptin resistance, thermoregulation and depression disorders. A diverse study of the reproductive disorders pathogenesis shows that fertility decrease is caused by the violation of the HPG regulation and MetS [32]. Reproductive disorders in turn potentiate the severity of metabolic disorders and, thus, forms a closed circle.

In women with MetS there is a decrease in the quality and number of oocytes, a violation of the menstrual cycle, a decrease in the receptivity of the endometrium, which leads to a infertility decrease [32]. Patients with MetS often demonstrate the ovarian polycystic syndrome [33] and reproductive losses, premature births, they have low the chances of giving birth to a living child and increased risk of the development of postpartum depression [34]. Obesity during pregnancy may increase the risk the mothers` MetS and may be the cause of fetus spina bifida, congenital heart defects and other congenital anomalies [35]. Children born by obese mothers have increased risks of obesity, cardiovascular diseases and diabetes mellitus in an adult [36].

The prevalence of obesity grows from year to year among women and men. In Ukraine according to the Ministry of Health data the frequency of obesity among women was 15.92‰ and among men 8.10 ‰ in 2017 (in 2002 it was 10,13 and 4,65 ‰, correpondingly), so obesity frequency has grown 1.6 times among women and 1.7

times among men. The obesity frequency among adolescents has grown 2.4 times (from 12.4 to 30.1 ‰) during 2005-2017.

Mechanisms of female infertility and reproductive losses among women with MetS are well known, but male infertility is less studied, although the connection of MetS and the male infertility prevalence is confirmed [37-38]. Studies show a strong association between MetS and hypogonadism, bad sperm morphology, somatization and depression. The men with MetS demonstrate reduced testosterone and sex hormone-binding levels, reduced sperm fertility and erectile dysfunction. The hypertension influence on male infertility is being discussed [37-38].

The ways of reproductive function improvement among patients with metabolic syndrome / obesity

The reproductive health of MetS patients could be improved by, interventions lowering weight, increase of motor activity, various diets, pharmacological preparations and bariatric surgery.

This publication is devoted to the analysis of lifestyle modifications by increasing motor activity and food habits changes. Healthy lifestyle is the most important intervention to prevent unwanted consequences of Mets on health and fertility of men [39, 40]. A number of research shows a positive correlation between weight loss, based on regular motor activity and food calorage decrease, and testosterone increase, the total number of sperm and sperm mobility increase. The positive effect was determined not only when limiting the food calorage, but also in consumption of seafood, poultry, nuts, whole grains, fruits and vegetables, antioxidant drugs and increase the consumption of omega-3 fatty acids [40]. However, today there are no specific clinical recommendations for the treatment of male infertility in MetS patients, although the importance of lifestyle modification in the treatment of male infertility and erectile dysfunction is presented in the recommendations of Diagnosis and Treatmen to Infertility in Men: AUA / ASRM GUIDELINE with level of evidence B and C [41 -42].

Studies show that reducing body weight and insulin resistance and correction of other metabolic disorders in women affirms not only the basic disease, but also the reproductive health, so life modification is recommended by WHO, American

Association of Clinical Endocrinologists and other organizations [43-44]. As a result of lifestyle modification and 5-10% weight loss, the frequency of spontaneous pregnancies grew up [45]. Meta-analysis [46], which assessed anthropometric, fertile, obstetric and fetal results of lifestyle modification showed that body weight decrease women lead to the growing frequency of pregnancies that came naturally, but this study did not reveal a significant influence of this intervention to others reproductive events. This could be explened by a mixed design of researches, which, included pharmacological preparations and lifestyle changes.

It is known that mother's healthy feed nutrition during pregnancy reduces the risks of gestational diabetes and child overweight. Some studies demonstrate the advantages of various protein diets, while others recommend the use of the Mediterranean diet [47]. The multiplicity of nutrition in an aspect of body weight loss in patients with MetS is being discussed.

We support the point that each patient with MetS requires an individual destination from a dietitian doctor taking into account the needs of the body and compulsory clarification of the principles of healthy eating. A balanced diet should be prescribed, it should satisfy the energy needs of the body and containe an adequate number of proteins, fats, carbohydrates, trace elements and vitamins. Particular attention should be payed to giving folic acid to the women of reproductive age, both to ensure the internal needs of the organism, and for the prevention of defects in the nerve tube in the fetus [48].

Regular physical activity in women and men can counteract the negative MetS impact and improve reproductive functions, even reduce the risk of developing MetS in descendants by epigenetic effects on the phenotypes modification [49]. The greatest effect is carried out by a moderate type aerobic load.

According to American Diabetes Association, the minimum physical activity should be 150 minutes / week, and according to National Institute for Health and Care Excellence recommendations, obese and overweight body patients are recommended 225-300 minutes / week of moderate-type motor activity, which is equivalent to the energy consumption of 1800- 2500 kcal / week [50]. It can be walks, swimming, aqua aerobics. But physical activity should be increased gradually and in accordance with

the recommendations of a doctor, before starting training, it is necessary to determine whether a patient requires special adaptations for exercise exercises.

Before the lifestyle modification you must know whether the patient has strong motivation to follow the recommended regime. A psychotherapist consultation could be recomended, behavioral therapy could be carried out in order to consolidate motivation and education of self-control skills [51].

Conclusions. Consequently, the weight loss, adequate physical activity and proper nutrition are leading non-pharmacological factors of treatment of reproductive disorders in patients with metabolic syndrome. Today, the study of a positive impact of lifestyle correction is relevant, optimal tactics should be elaborated in with the multidisciplinary team of doctors.

References

1. Saklayen MG. The Global Epidemic of the Metabolic Syndrome / M.G.Saklayen //CurrHypertens Rep. – 2018. –T.20, N.2. – P.12. Режимдоступу: doi: 10.1007/s11906-018-0812-z.
2. Pucci G. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature / G.Pucci, R.Alcidi, L. Tap et al. //Pharmacol Res. – 2017. –N.120. – P.34-42. Режимдоступу: doi: 10.1016/j.phrs.2017.03.008.
3. Macaluso M, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A, Berman SM, Wang RY, Farr SL, Pollack LA. A public health focus on infertility prevention, detection, and management. FertilSteril. 2010 Jan;93(1):16.e1-10. doi: 10.1016/j.fertnstert.2008.09.046.
4. Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM, Toppari J, Andersson AM, Eisenberg ML, Jensen TK, Jørgensen N, Swan SH, Sapra KJ, Ziebe S, Priskorn L, Juul A. Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility. Physiol Rev. 2016 Jan;96(1):55-97. doi: 10.1152/physrev.00017.2015.
5. Casteel CO, Singh G. Physiology, Gonadotropin-Releasing Hormone. [Updated 2020 Jun 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558992/
6. Evans MC, Anderson GM. Neuroendocrine integration of nutritional signals on reproduction. J Mol Endocrinol. 2017 Feb;58(2):R107-R128. doi: 10.1530/JME-16-0212.
7. Tena-Sempere M. Interaction between energy homeostasis and reproduction: central effects of leptin and ghrelin on the reproductive axis. HormMetab Res. 2013 Dec;45(13):919-27. doi: 10.1055/s-0033-1355399.

8. Carmo-Silva S, Cavadas C. Hypothalamic Dysfunction in Obesity and Metabolic Disorders. Adv Neurobiol. 2017;19:73-116. doi: 10.1007/978-3-319-63260-5_4.

9. Montagnoli C, Zanconato G, Cinelli G, Tozzi AE, Bovo C, Bortolus R, Ruggeri S. Maternal mental health and reproductive outcomes: a scoping review of the current literature. Arch Gynecol Obstet. 2020 Oct;302(4):801-819. doi: 10.1007/s00404-020-05685-1.

10. Dixon-Mueller R. The sexuality connection in reproductive health. Stud Fam Plann. 1993 Sep-Oct;24(5):269-82. Senapati S. Infertility: a marker of future health risk in women? FertilSteril. 2018 Oct;110(5):783-789. doi: 10.1016/j.fertnstert.2018.08.058

11. Vannuccini S, Clifton VL, Fraser IS, Taylor HS, Critchley H, Giudice LC, Petraglia F. Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. Hum Reprod Update. 2016 Jan-Feb;22(1):104-15. doi: 10.1093/humupd/dmv044.

12. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem. 2018 Dec;62:2-10. doi: 10.1016/j.clinbiochem.2018.03.012.

13. Zhou L, Han L, Liu M, Lu J, Pan S. Impact of metabolic syndrome on sex hormones and reproductive function: a meta-analysis of 2923 cases and 14062 controls. Aging (Albany NY). 2020 Dec 1;13(2):1962-1971. doi: 10.18632/aging.202160

14. Ventimiglia E, Capogrosso P, Serino A, Boeri L, Colicchia M, La Croce G, Scano R, Papaleo E, Damiano R, Montorsi F, Salonia A. Metabolic syndrome in White-European men presenting for secondary couple's infertility: an investigation of the clinical and reproductive burden. Asian J Androl. 2017 May-Jun;19(3):368-373. doi: 10.4103/1008-682X.175783.

15. Zhao L, Pang A. Effects of Metabolic Syndrome on Semen Quality and Circulating Sex Hormones: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2020 Aug 11;11:428. doi: 10.3389/fendo.2020.00428.

16. He Y, Lu Y, Zhu Q, Wang Y, Lindheim SR, Qi J, Li X, Ding Y, Shi Y, Wei D, Chen ZJ, Sun Y. Influence of metabolic syndrome on female fertility and in vitro fertilization outcomes in PCOS women. Am J Obstet Gynecol. 2019 Aug;221(2):138.e1-138.e12. doi: 10.1016/j.ajog.2019.03.011.

17. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. FertilSteril. 2017 Apr;107(4):840-847. doi: 10.1016/j.fertnstert.2017.01.017. Klenov VE, Jungheim ES. Obesity and reproductive function: a review of the evidence. CurrOpinObstet Gynecol. 2014 Dec;26(6):455-60. doi: 10.1097/GCO.0000000000000113.

18. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017;390:2627–42

19. WHO. Report of the Commission on Ending Childhood Obesity: implementation plan: executive summary. Geneva: World Health Organization; 2017 (http://www.who.int/end-childhood-obesity/ publications/echo-plan-executive-summary/en/)

20. Thong EP, Codner E, Laven JSE, Teede H. Diabetes: a metabolic and reproductive disorder in women. Lancet Diabetes Endocrinol. 2020 Feb;8(2):134-149. doi: 10.1016/S2213-8587(19)30345-6.

21. Trikudanathan S. Polycystic ovarian syndrome. Med Clin North Am. 2015 Jan;99(1):221-35. doi: 10.1016/j.mcna.2014.09.003. Talmor A, Dunphy B. Female obesity and infertility. Best Pract Res Clin ObstetGynaecol. 2015 May;29(4):498-506. doi: 10.1016/j.bpobgyn.2014.10.014.

22. Wilkes S, Murdoch A. Obesity and female fertility: a primary care perspective. J Fam PlannReprod Health Care. 2009 Jul;35(3):181-5. doi: 10.1783/147118909788707995.

23. Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. J Womens Health (Larchmt). 2015 Apr;24(4):299-307. doi: 10.1089/jwh.2014.5000.

24. Kahn BE, Brannigan RE. Obesity and male infertility. CurrOpin Urol. 2017 Sep;27(5):441-445. doi: 10.1097/MOU.0000000000000417.

25. Maggi R, Cariboni AM, Marelli MM, Moretti RM, Andrè V, Marzagalli M, Limonta P. GnRH and GnRH receptors in the pathophysiology of the human female reproductive system. Hum Reprod Update. 2016 Apr;22(3):358-81. doi: 10.1093/humupd/dmv059.

26. Yan W, Cheng L, Wang W, Wu C, Yang X, Du X, Ma L, Qi S, Wei Y, Lu Z, Yang S, Shao Z. Structure of the human gonadotropin-releasing hormone receptor GnRH1R reveals an unusual ligand binding mode. Nat Commun. 2020 Oct 20;11(1):5287. doi: 10.1038/s41467-020-19109-w.

27. Barua M, Van Driel F, Jansen W. Tuberculosis and the sexual and reproductive lives of women in Bangladesh. PLoS One. 2018 Jul 19;13(7):e0201134. doi: 10.1371/journal.pone.0201134.

28. Segal TR, Giudice LC. Before the beginning: environmental exposures and reproductive and obstetrical outcomes. FertilSteril. 2019 Oct;112(4):613-621. doi: 10.1016/j.fertnstert.2019.08.001.

29. Practice Committee of the American Society for Reproductive Medicine. Smoking and infertility: a committee opinion. FertilSteril. 2018 Sep;110(4):611-618. doi: 10.1016/j.fertnstert.2018.06.016.

30. Rooney KL, Domar AD. The relationship between stress and infertility. Dialogues Clin Neurosci. 2018 Mar;20(1):41-47. doi: 10.31887/DCNS.2018.20.1/klrooney.

31. Paliychuk OV, Polishchuk LZ, Rossokha ZI, Chekhun VF. Molecular-genetic models for prognosis of development of tumors of reproductive system in women with family history of cancer. Exp Oncol. 2018 Mar;40(1):59-67.

32. Michalakis K, Mintziori G, Kaprara A, Tarlatzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. Metabolism. 2013 Apr;62(4):457-78. doi: 10.1016/j.metabol.2012.08.012.

33. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. Trends Endocrinol Metab. 2015 Mar;26(3):136-43. doi: 10.1016/j.tem.2014.12.003

34. Silveira ML, Ertel KA, Dole N, Chasan-Taber L. The role of body image in prenatal and postpartum depression: a critical review of the literature. Arch WomensMent Health. 2015 Jun;18(3):409-21. doi: 10.1007/s00737-015-0525-0.

35. Wax JR. Risks and management of obesity in pregnancy: current controversies. CurrOpinObstet Gynecol. 2009 Apr;21(2):117-23. doi: 10.1097/GCO.0b013e328328d3c7.

36. Frias AE, Grove KL. Obesity: a transgenerational problem linked to nutrition during pregnancy. SeminReprod Med. 2012 Dec;30(6):472-8. doi: 10.1055/s-0032-1328875.

37. Morrison CD, Brannigan RE. Metabolic syndrome and infertility in men. Best Pract Res Clin ObstetGynaecol. 2015 May;29(4):507-15. doi: 10.1016/j.bpobgyn.2014.10.006.

38. Martins AD, Majzoub A, Agawal A. Metabolic Syndrome and Male Fertility. World J Mens Health. 2019 May;37(2):113-127. doi: 10.5534/wjmh.180055.

39. Warner L, Jamieson DJ, Barfield WD. CDC releases a National Public Health Action Plan for the Detection, Prevention, and Management of Infertility. J Womens Health (Larchmt). 2015 Jul;24(7):548-9. doi: 10.1089/jwh.2015.5355.

40. Nassan FL, Chavarro JE, Tanrikut C. Diet and men's fertility: does diet affect sperm quality? FertilSteril. 2018 Sep;110(4):570-577. doi: 10.1016/j.fertnstert.2018.05.025.

41. Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, Mulhall JP, Niederberger C, Sandlow JI, Sokol RZ, Spandorfer SD, Tanrikut C, Treadwell JR, Oristaglio JT, Zini A. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. J Urol. 2021 Jan;205(1):36-43. doi: 10.1097/JU.0000000000001521.

42. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, Heidelbaugh J, Khera M, McVary KT, Miner MM, Nelson CJ, Sadeghi-Nejad H, Seftel AD, Shindel AW. Erectile Dysfunction: AUA Guideline. J Urol. 2018 Sep;200(3):633-641. doi: 10.1016/j.juro.2018.05.004.

43. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016 Nov;22(6):687-708. doi: 10.1093/humupd/dmw025.

44. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E; American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE); Androgen Excess and PCOS Society. American association of clinical endocrinologists, American college of endocrinology, and androgen excess and PCOS society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2. EndocrPract. 2015 Dec;21(12):1415-26. doi: 10.4158/EP15748.DSCPT2.

45. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2012 Nov-Dec;18(6):618-37. doi: 10.1093/humupd/dms030.

46. Lan L, Harrison CL, Misso M, Hill B, Teede HJ, Mol BW, Moran LJ. Systematic review and meta-analysis of the impact of preconception lifestyle

interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women. Hum Reprod. 2017 Sep 1;32(9):1925-1940. doi: 10.1093/humrep/dex241.

47. Timmermans S, Steegers-Theunissen RP, Vujkovic M, den Breeijen H, Russcher H, Lindemans J, Mackenbach J, Hofman A, Lesaffre EE, Jaddoe VV, Steegers EA. The Mediterranean diet and fetal size parameters: the Generation R Study. Br J Nutr. 2012 Oct 28;108(8):1399-409. doi: 10.1017/S000711451100691X.

48. Cawley S, Mullaney L, McKeating A, Farren M, McCartney D, Turner MJ. A review of European guidelines on periconceptional folic acid supplementation. Eur J Clin Nutr. 2016 Feb;70(2):143-54. doi: 10.1038/ejcn.2015.131.

49. Tibana RA, Franco OL, Pereira RW, Navalta J, Prestes J. Exercise as an Effective Transgenerational Strategy to Overcome Metabolic Syndrome in the Future Generation: Are We There? Exp Clin Endocrinol Diabetes. 2017 Jun;125(6):347-352. German. doi: 10.1055/s-0042-120538.

50. Stegenga H, Haines A, Jones K, Wilding J; Guideline Development Group. Identification, assessment, and management of overweight and obesity: summary of updated NICE guidance. BMJ. 2014 Nov 27;349:g6608. doi: 10.1136/bmj.g6608.

51. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognit Ther Res. 2012 Oct 1;36(5):427-440. doi: 10.1007/s10608-012-9476-1.

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