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Androgen excess, female infertility and bone mineral density: a review

Nadmiar androgenów, niepłodność żeńska i gęstość mineralna kości: przegląd piśmiennictwa

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Many conditions with androgen excess are correlated with fertility disorders and changes in bone mineral density. This can result in infertility and changes in bone mineral density which are also a risk factor for osteopenia and osteoporosis. The most frequently encountered diseases are: polycystic ovary syndrome (PCOS) and congenital adrenal hyperplasia (CAH). This paper describes above mentioned disorders and their influence on the reproductive and bone system.

Wiele schorzeń przebiegających ze zwiększonym poziomem androgenów we krwi przebiega z zaburzeniami płodności i zmianami w składzie mineralnym kości, powodując tym samym bezpłodność i stanowiąc bezpośrednie zagrożenie dla rozwoju osteopenii oraz osteoporozy w przyszłości. Wśród tych schorzeń najczęstsze są: zespół policystycznych jajników (PCOS) oraz wrodzony przerost nadnerczy (CAH). Poniższa praca przedstawia omówienie wyżej wymienionych zaburzeń i ich wpływ na układ rozrodczy oraz kostny.

Introduction

The purpose of this review is to integrate understanding of infertility in women with hyperandrogenism. In this article most important is the fact, that infertility is often caused by diseases, in which androgen excess occur. The second point of this work is to present treatment methods of infertility in androgen excess disorders, of which the most frequently encountered are: polycystic ovary syndrome (PCOS) and congenital adrenal hyperplasia (CAH).

Hyperandrogenemia means elevated androgen levels [1]. The majority of the abnormal values circulate in the form of free testosterone (T), with the sole measurement of total T with all limitations of measurement methods [2]. There are many controversies concerning the measurement methods of free and total testosterone in women [3,4]. For example, salivary testosterone has been tested as an alternative method of androgen level measurement in women [5].

The significance of androstenedione also remains unclear, but it might increase the number of subjects identified as hyperandrogenic [6]. Some of patients will demonstrate supranormal levels of the androgen metabolite dehydroepiandrosterone sulfate (DHEAS)- a weak androgen primarily produced by adrenal glands. Unfortunately, measuring its level in plasma has a limited diagnostic value.

In general, clinical features of hyperandrogenism include following sypmtoms: hirsutism, acne, androgenic alopecia, ovulatory dysfunction, infertility, oligo/amenorrhea or manifestation of virilisation (male pattern hair growth, clitoromegaly, deepening of the voice) [7]. In patients in whom hirsutism is not related to medication use, evaluation is focused on testing for polycystic ovary syndrome, congenital adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, hyperprolactinemia and androgen-secreting tumors. It is important that there are also many medications causing hirsutism (bupropion, carbamazepine, clonazepam, corticosteroids, cyclosporine, diazoxide, donepezil, fluoxetine, lamotrigine, mycophenolate, olanzapine) [8].

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder in premenopausal women [9], which affects about 20% of women of reproductive age [10]. PCOS is a hyperandrogenic disorder that is characterized by a constellation of signs and symptoms, including clinical and/or biochemical hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology in ultrasonography [11]. Although the criteria for the diagnosis of PCOS have been a matter of intense debate for many decades, all the current definitions the 1990 National Institute of Child Health and Human Development criteria [11], the 2003 European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine definition [12], and the 2006 Androgen Excess Society evidence-based definition [13]) agree that the exclusion of other disorders with clinical presentation of hyperandrogenism, including androgen secreting tumors, hyper- or hypothyroidism,

hyperprolactinemia, Cushing's syndrome, and nonclassiacal congenital adrenal hyperplasia (NCAH) is required. Obesity, abdominal obesity, and weight gain in teenage and adult women can be used as predictors of the future presence of hirsutism and menstrual irregularities in PCOS [14]. Obesity plays an important role in the development of hyperandrogenism and chronic anovulation [15]. It is also associated with abnormalities of sex steroid metabolism, such as increased androgen production and suppression of sex hormone–binding globulin (SHBG) [16]. Obese patients with PCOS have more severe cardiovascular and metabolic risk factors than their lean counterparts [17]. Increased body weight might modify the PCOS phenotype, raise both metabolic and cardiovascular risk, and determine anovulation [18,19]. Moreover, PCOS is strongly associated with gestational diabetes. It should be noted that PCOS is a heterogeneous and inconsistent condition. Additional obesity increases obstetric and neonatal risk of miscarriage, preterm delivery, shoulder dystocia, postpartum hemorrhage and infection. Women with PCOS have increased risk of pregnancy complications (hypertension, growth restriction or macrosomia) in PCOS population [20].

Polycystic ovary syndrome is also a primary cause of anovulatory infertility. Obesity is commonly found in women with PCOS and is associated with resistance to induction of the ovulation. The very primary treatment for anovulatory infertility in obese women with PCOS is weight loss [21]. It should be in the first place reached by behavioral modifications (diet, exercise), secondary therapies include pharmacogical treatment or surgical interventions [22]. Changes in the lifestyle positively affect body composition, hyperandrogenism (high male hormones and clinical effects) and insulin resistance in women with PCOS. There were no evidences of effect for lifestyle intervention on improving glucose tolerance or lipid profiles, and no literature assessing clinical reproductive outcomes and patients' satisfaction [23]. Additionally, women with PCOS present lower scores in domains of health- related quality of life (HRQoL), especially in the emotional role function [24]. Acupuncture and physical activity seem to improve those scores. Authors also suggest that mental health of women with PCOS requires further investigations [25]. Short-term (4–5-month diet and exercise) interventions have also shown to improve the menstrual cyclicity (40-70%), and about 35% patients confirmed ovulation. An addition of exercise may improve body composition, but it did not improve menstrual cyclicity or ovulatory function compared to diet alone [36].

Weight loss following bariatric surgery in women with PCOS appears to restore ovulation and menstrual function in most women with PCOS [27].

Clomiphene citrate, a selective estrogen receptor modulator (SERM), has been known as the first-line treatment for ovulation induction for many years. By the negative feedback result in increasing of gonadotropin-releasing hormone (GnRH) and follicle-stimulating hormone (FSH), clomiphene leads to follicle development and ovulation. Although it is more effective (significantly higher live births) in women with normal weight, it can be also used among PCOS women [28].

The therapy with clomiphene citrate should last up to 6-month, as pregnancy rates are not higher with advancing cycles. The initial dose of clomiphene citrate is 50 mg for 5 days beginning on cycle days. Later it may be increased up to a maximal dose of 150 mg per day until an ovulatory response is achieved. Adjunctive treatment with dexamethasone has not yet been proven beneficial as the first-line treatment [22], but with metformin it seems to have a positive effect on hyperandrogenic patients [29]. Alternative for ovulation induction are: aromatase inhibitors, letrozole and anastrozole, and selective estrogen receptor modulators, such as tamoxifen [30]. These agents are considered to be a second-line agents.

For many years the insulin-sensitizing agents such as biguanide (metformin) and the thiazolidinediones were used for ovulation induction in order to help regulate menses and mitigate symptoms in women with PCOS [31]. In 2008, the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM)-Sponsored PCOS Consensus Workshop Group reviewed the data and concluded metformin should be restricted to women with glucose intolerance [22]. A Cochrane review in 2012 analyzed 38 RCTs using metformin for ovulation induction and concluded that there is no evidence that metformin improves live birth rates, no matter if it is used alone or in combination with clomiphene citrate [32]. Another multicenter, randomized trial evaluated the use of metformin as a pretreatment for 3 months in order to restore ovulation. If the pregnancy did not occur, ovulation induction was commenced with clomiphene citrate up to pregnancy or 6 unsuccessful cycles. After that other methods were used. There was a significant higher live birth rate and pregnancy rate in the metformin group, compared to placebo during the period of ovulation induction [33].

The goal of gonadotropin therapy for women with PCOS is to provide an FSH level to initiate and continue a proper mono-follicular development, simultaneously not to perform superovulation. The risk of gonadotropin therapy is thus multifollicular recruitment with subsequent ovarian hyperstimulation syndrome and/or multiple gestations [34]. The 2008 Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group recommends the step-up method based on results from the largest study demonstrating a greater monofollicular response [22]. Gonadotropin stimulation requires monitoring with a serial ultrasound and serum estradiol levels.

Laparoscopic ovarian drilling is currently the most common surgical procedure to treat PCOS women and can be performed either with laser or electrocautery [35]. Laparoscopic ovarian drilling restores ovulation in about 50% of women and improves menstrual regularity. Decreased androgen plasma levels and the luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio are reported to normalize following the procedure.

Another method of treatment is an in-vitro fertilization (IVF) which is often offered to clomiphene- resistant women with PCOS. The 2008 Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group recommended IVF as the third-line treatment after step-up gonadotropin protocols [22]. Metformin does not improve pregnancy rates with IVF, but has been shown to reduce the rate of severe ovarian hyperstimulation syndrome [36]. The retrospective IVF study demonstrated a significant reduction in pregnancy and live birth rates in obese women [37].

Last but not least and definitely worth paying attention, is the issue of bone mineral density in women with PCOS. The characteristic hormone profile affecting bones in this condition includes:

1. Elevated testosterone and androstenedione level which may have a positive influence on bones.
2. Static 17β-estradiol level, without an estradiol surge (which affects the ovulation process) and expected to have a negative influence on bones.
3. Hyperinsulinemia which has been shown to have a positive influence on bone mineral density by activation of osteocalcin and osteoblasts stimulation [38,39,40].

Osteoporosis is characterized by low bone mass and architectural deterioration of the bone, caused mostly by post-menopausal estrogen decrease, calcium and vitamin D deficiency, aging and many others. Decreased BMD is commonly known as osteopenia. At first sight androgen excess and hyperinsulinemia should compensate for the negative effects of estrogens and amenorrhea on bone mineral density. Estrogens and androgens interact with each other to determine the final BMD, already during puberty. Among women with androgen excess this process is modified and lasts longer. The majority of studies show however, that primarily positive effect of androgens is suppressed or normalized by estrogen deficiency. Women with PCOS show rather BMD comparable to healthy population [41,42]. However, there are studies stating, that the deciding factors in determining BMD could be obesity and hyperinsulinemia.

Non-obese PCOS women show lower BMD and obese women have BMD comparable to the healthy ones [43]. Also contraceptive drugs might cause the decrease of the BMD among PCOS patients [44].

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by mutations in genes encoding the enzymes involved in the adrenal synthesis of cortisol [45] which results in decreased cortisol production and increased secretion of ACTH. The excessive synthesis of precursor steroids due to increased ACTH secretion leads to androgen excess. Main causes are 21-hydroxylase (affecting both alleles of CYP21) or 11β-hydroxylase affecting both alleles of CYP11B1) deficiencies [45]. In CAH, failure in cortisol synthesis results in reduced cortisol feedback and consequently increased pituitary ACTH release, which promotes over secretion of 17-hydroxyprogesterone (17OHP), progesterone, and adrenal androgens. When mutations of the genes cause a complete or almost complete deficiency of the enzymes, the classical presentation is the virilization in female newborns, which may also be presented in both sexes (male and female newborns) with salt wasting and hyperkalemia [45,46]. Abnormal hormonal secretion manifests with impaired sex development in girls, precocious pseudopuberty and short stature. In adulthood with hirsutism in females and fertility problems in both sexes. CAH is a life-long chronic disorder. In childhood, treatment focuses on issues of gender assignment, genital surgery and optimization of growth and pubertal development. Priorities change with increasing age, typically focusing on fertility in early adult life and prevention of metabolic syndrome and osteoporosis in middle and older age, respectively. The clinical symptoms of CAH are hirsutism, acne and menstrual disorders [45,47]. Menarche occurs spontaneously in 80% of female patients at a median age of 13 (range 9–25) years [48]. Traditionally, reduced fertility rates have been reported in women with classic CAH, especially in those with the salt-wasting phenotype. Subfertility in females with classic CAH is a consequence of several contributing factors, including androgen excess, adrenal progesterone hypersecretion, consequences of genital reconstructive surgery, secondary polycystic ovaries syndrome and psychosexual factors [49]. Irregular menstruation as an indication of anovulation was reported in 61% CAH women [50]. A number of factors have been suggested as the reasons for the low fertility among women with CAH [51,52] such as: delayed psychosexual development, low sexual activity, adrenal overproduction of androgens and progestins, PCOS, neuro-endocrine factors and genital surgery. The low pregnancy rates has been the subject of many reports [51,53,54]. Lo and Grumbach reviewed the literature published between 1956–2000 and reported on 105 pregnancies resulting in the birth of 73 children in women with virilizing adrenal hyperplasia [53]. It has been debated whether corticosteroid doses should be increased during pregnancy [55,56]. Cushing's syndrome, androgen secreting tumors, drug-induced hirsutism, hyperprolactinemia and congenital adrenal hyperplasia should be excluded by basal and stimulated serum test and CT/MRI scans. In women presenting ACTH-stimulated 17-hydroxyprogesterone plasma levels more than or equal to 10 ng/ml, NCAH should be additionally confirmed by molecular genetic analysis [57,58]. The aim of the theraphy is to normalize ACTH and reduce androgen levels. The therapy should not result in excessed glucocorticoid exposure with associated complications including short stature, obesity, hypertension, and an adverse metabolic profile. In classic CAH, lifelong glucocorticoid and often also mineralocorticiod therapy are mandatory, whereas in the milder NC form, treatment is given when patients have symptoms such as hirsutism, oligo-amenorrhoea or infertility. If corticosteroid supplementation is insufficient, androgen production from the adrenals will increase and suppress gonadotrophin secretion from the pituitary and that will lead to a disturbance of the ovarian cycle resulting in anovulation and infertility [49,58].

When it comes to the BMD issue, it is lower than or comparable to, in almost all the patients with CAH and in heathy population. Majority of the researches published so far have evaluated children and only some of them describe alternations in BMD among adults [59-63]. Although adrenal androgens are said to play a positive role in the bone mineralization process [64], there is still an issue of oral glucocorticosteroids (supplementation) that have a negative impact on bone mineral status [63]. Also patients with the classic form of CAH have lower BMD than those with a non-classic form of CAH [60]. Both man and woman have an icreased risk of fractures and osteoporosis [61,62]. This is why the supplementation should be carried out with an optimal dose of glucocorticosteroids, with monitoring of the BMD status and proper osteoporosis prophylaxis.

Cushing's syndrome describes the signs and symptoms associated with prolonged exposure to inappropriately high levels of the cortisol. This can be caused by taking glucocorticoid permanently or diseases that result in excess cortisol level, adrenocorticotropic hormone or corticotropin-releasing hormone levels [65]. Cushing's disease refers to a pituitary-dependent cause of Cushing's syndrome: adenoma of the pituitary gland produces large amounts of ACTH, causing the adrenal glands to produce elevated levels of cortisol. It is the most common non-iatrogenic cause of Cushing's syndrome, responsible for 70% of cases excluding glucocorticoid-related cases. An easy way to distinguish Cushing's syndrome (primary hypercortisolism, specifically) from Cushing's disease is that the measured ACTH levels in plasma are low. The decrease in ACTH is due to increased negative feedback of cortisol on the hypothalamus and anterior pituitary [66]. Symptoms of Cushing's syndrome include weight gain, particularly with central obesity, excess sweating, teleangiectasia, thinning of the skin and mucous membranes, purple or red striae and hirsutism, reduced libido, menstrual disturbances and infertility in women due to elevations in adrogens levels in plasma [67]. Other signs include persistent metabolic disturbances like: hypertension, insulin resistance or diabetes. Hypercortisolemia leads to serious complications for mother and foetus, and is associated with premature labor and high foetal mortality [68].

Studies evaluating bone turnover in patients with Cushing's syndrome are consistent and prove, that the BMD is decreased and the function of osteoblasts is reduced [69,70,71]. These patients are in an increased risk of osteoporosis, osteopenia and fractures, whereby osteoporosis affects about 50% of them and is the most common cause of secondary osteoporosis [72]. It was proven, that the bone turnover and severity of osteoporosis depends on the etiology of Cushing's syndrome - more severe cases and increased bone turnover can be seen among patients with primary adrenal than pituary-dependent disease [72,73]. Also patients with an ectopic ACTH secretion have higher values of cortisol level than other groups with endogenous hypercortisolemia [74]. Another study shows however, that the duration and degree of hypercortisolism influence bone status the most [75]. All the researches confirm that cortisol excess plays the most important role in bone impairment. Gonadal status seems to be of less importance[75,76].

Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary axis. Prolactinoma may be an important cause for androgen excess. Although elevated plasma prolactin levels are highly suggestive of a prolactinoma, other causes of hyperprolactemia like hypothyroisim, Cushing's disease, medications should be excluded [77]. Patients typically present with hypogonadism, infertility, hypogonadism, galactorrhea, osteoporosis or, in the case of macroadenomas, symptoms related to mass effect (headache and visual field defects) [78].
A prolactin excess can affect bones due

to increased bone turnover. One of the main causes of hyperprolactinemia are prolactinoma and estrogen deficiency. Patients with this condition often suffer from decreased BMD and osteoporosis. It was shown, that the severity of this condition correlates positively with longer duration of the disease [79,80]. Increased vertebral fracture incidence was noted in both women and man [81,82].

Androgen-secreting tumors are rare in women with hirsutism, comprising 0.2 percent of cases in two studies of women presenting with clinical hyperandrogenemia [15,83]. Neoplasms may be adrenal or ovarian in origin, and often cause high elevations in androgen plasma level. More than one-half of them is malignant. Rapid onset of hirsutism, virilization, or a palpable abdominal or pelvic mass are typical for an androgen-secreting tumor [84]. Conditions associated with low ovarian hormones levels are among others osteopenia and osteoporosis. Only one research carried out on 14 patients describes an influence of ovarian secreting tumors on BMD [85]. They seem to play a protective role to decreased BMD.

Conclusion

In summarizing, androgen excess has a negative influence on both fertility and bone system. Patients with hyperandrogenism are often infertile, suffer from more serious pregnancy complications and are also in a risk of preterm birth, miscarriage and many others. Additionally, the majority of them have lower BMD, suffer from osteopenia or osteoporosis when compared to the healthy population. It should be noticed, that this conditions are preventable and sometimes treatable with an appropriate diet, exercises and medical treatment.

References

1. Field HP, Wheeler MJ. The measurement of androgens. Methods Mol Biol 2013; 1065:211-226.

2. Shea JL, Wongt PY, Chen Y. Free testosterone: clinical utility and important analytical aspects of measurement. Adv Clin Chem 2014;63:59-84.

3. Niki H, Matsuzaki T, Kinouchi R, Iwasa T, Kawami T, Kato T, Kuwahara A, Irahara M. Improvement in diagnostic performance of the revised total testosterone measuring system in Japanese women with polycystic ovary syndrome. J Med Invest 2014; 61:65-71.

4. Spritzer PM. Polycystic ovary syndrome: reviewing diagnosis and management of metabolic disturbances. Arq Bras Endocrinol Metabol 2014; 58:182-187.

5. Szydlarska D, Grzesiuk W, Kondracka A, Bartoszewicz Z, Bar-Andziak E. Measuring salivary androgens as a useful tool in the diagnosis of polycystic ovary syndrome. Endokrynol Pol 2012; 63:183-190.

6. Rachoń D. Differential diagnosis of hyperandrogenism in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2012; 120:205-209.

7. Agapova SE, Cameo T, Sopher AB, Oberfield SE. Diagnosis and challenges of polycystic ovary syndrome in adolescence. Semin Reprod Med 2014; 32:194-201.

8. Bode D, Seehusen DA, Baird D. Hirsutism in women. Am Fam Physican 2012; 85:373-380.

9. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2013; 6:1-13.

10. Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91:1357-1363.

11. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome. In: Givens JHF, Merriman G, editors. The Polycystic Ovary Syndrome. Cambridge, MA: Blackwell Scientific; 1992. 377–384.

12. Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group 2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.

13. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91:4237–4245.

14. 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;89:2745–2749.

15. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, Taylor K, Boots LR. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab 2004; 89:453–262.

16. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010; 95:2038-2049.

17. Schmidt J, Landin-Wilhelmsen K, Brannstrom M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab 2011;96:3794–3803.

18. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod 2012; 27:3067–3073.

19.Cattrall FR, Healy DL. Long-term metabolic, cardiovascular and neoplastic risks with polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004;18:803–812.

20. Hu S, Leonard A, Seifalian A, Hardiman P. Vascular dysfunction during pregnancy in women with polycystic ovary syndrome. HumReprod 2007;22:1532–1539.

21. Domecq JP, Prutsky G, Mullan RJ, Hazem A, Sundaresh V, Elamin MB, Phung OJ, Wang A, Hoeger K, Pasquali R, Erwin P, Bodde A, Montori VM, Murad MH. Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. J Clin Endocrinol Metab 2013;98:4655-4663.

22. The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008;89:505–522.

23. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database of Syst Rev 2011;7:CD007689.

24. Li Y, Li Y, Yu Ng EH, Stener-Victorin E, Hou L, Wu T, Han F, Wu X. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. Fertil Steril 2011; 96:452-458.

25. Stener-Victorin E, Holm G, Janson PO, Gustafson D, Waern M. Acupuncture and physical exercise for affective symptoms and health-related quality of life in polycystic ovary syndrome: secondary analysis from a randomized controlled trial. BMC Complement Altern Med 2013;13:131.

26. Nybacka A, Carlstrom K, Stahle A, Nyren S, Hellstrom PM, Hirschberg AL. Randomized comparison of the influence of dietary management and/or physical exercise on ovarian function and metabolic parameters in overweight women with polycystic ovary syndrome. Fertil Steril 2011; 96:1508–1513.

27. 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; 90:6364–6369.

28. Figueiredo JB, Nastri CO, Vieira AD, Martins WP. Clomiphene combined with gonadotropins and GnRH antagonist versus conventional controlled ovarian hyperstimulation without clomiphene in women undergoing assisted reproductive techniques: systematic review and meta-analysis. Arch Gynecol Obstet 2013; 287:779-790.

29. Abu Hashim H, Foda O, Ghayaty E. Combined metformin-clomiphene in clomiphene-resistant polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand 2015 [In Press].

30. Badawy A, Gibreal A. Clomiphene citrate versus tamoxifen for ovulation induction in women with PCOS: a prospective randomized trial. Eur J Obstet Gynecol and Reprod Biol 2011;159:1151–1154.

31. Pasquali R, Gambineri A. Insulin sensitizers in polycystic ovary syndrome. Front Horm Res 2013; 40:83-102.

32. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev 2012;5:CD003053.

33. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A, Tapanainen JS. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind placebo-controlled randomized trial. J Clin Endocrinol Metabol 2012;97:1492–1500.

34. Perales-Puchalt A, Legro RS. Ovulation induction in women with polycystic ovary syndrome. Steroids 2013;78:767-772.

35. Elmashad A. Impact of laparoscopic ovarian drilling on anti-Mullerian hormone levels and ovarian stromal blood flow using three-dimensional power Doppler in women with anovulatory polycystic ovary syndrome. Fertil Steril 2011;95:2342–2346.

36. Palomba S, Falbo A, Carrillo L, Villani MT, Orio F, Russo T, Di Cello A, Cappiello F, Capasso S, Tolino A, Colao A, Mastrantonio P, La Sala GB, Zullo F, Cittadini E. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil Steril 2011;96:1384–1390.

37. Moragianni VA, Jones SM, Ryley DA. The effect of body mass index on the outcomes of first assisted reproductive technology cycles. Fertil Steril 2012; 98:102–108.

38. Stolk RP, Van Daele PL, Pols HA, Burger H, Hofman A, Birkenhäger JC, Lamberts SW, Grobbee DE. Hyperinsulinemia and bone mineral density in an elderly population: The Rotterdam Study. Bone 1996; 18:545-549.

39. Riddle RC, Clemens TL. Insulin, osteoblasts, and energy metabolism: why bone counts calories. J Clin Invest 2014; 124:1465-1467.

40. Zborowski JV, Cauley JA, Talbott EO, Guzick DS, Winters SJ. Clinical Review 116: Bone mineral density, androgens, and the polycystic ovary: the complex and controversial issue of androgenic influence in female bone. J Clin Endocrinol Metab 2000;85:3496-3506.

41. Adami S, Zamberlan N, Castello R, Tosi F, Gatti D, Moghetti P. Effect of hyperandrogenism and menstrual cycle abnormalities on bone mass and bone turnover in young women. Clin Endocrinol (Oxf) 1998;48:169-173.

42. Noyan V, Yucel A, Sagsoz N. The association of bone mineral density with insulin resistance in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2004;115:200-205.

43. To WW, Wong MW. A comparison of bone mineral density in normal weight and obese adolescents with polycystic ovary syndrome. J Pediatr Adolesc Gynecol 2012; 25:248-253.

44. Moran LJ, Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. Steroidal contraceptive use is associated with lower bone mineral density in polycystic ovary syndrome. Endocrine 2015 [In Press].

45. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocrine Rev 2000;21:245–291.

46. Pang S, Clark A. Newborn screening, prenatal diagnosis, and prenatal treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Trends Endocrinol Metab 1990; 1:300-307.

47. Honour JW. 17-Hydroxyprogesterone in children, adolescents and adults. Ann Clin Biochem 2014; 51:424-240.

48. Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, Han TS, Carroll PV, Conway GS, Rees DA, Stimson RH, Walker BR, Connell JM, Ross RJ. United Kingdom Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE). Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab 2010;95:5110-5121.

49. Kamoun M, Feki MM, Sfar MH, Abid M. Congenital adrenal hyperplasia: Treatment and outcomes. Indian J Endocrinol Metab 2013;17:14-17.

50. Bachelot A, Plu-Bureau G, Thibaud E, Laborde K, Pinto G, Samara D, Nihoul-Fékété C, Kuttenn F, Polak M, Touraine P. Long-term outcome of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Horm Res 2007; 67:268-276.

51. Jääskeläinen J, Hippeläinen M, Kiekara O, Voutilainen R. Child rate, pregnancy outcome and ovarian function in females with classical 21-hydroxylase deficiency. Acta Obstet Gynecol Scand 2000;79:687-692.

52. Otten BJ, Stikkelbroeck MM, Claahsen-van der Grinten HL, Hermus AR. Puberty and fertility in congenital adrenal hyperplasia. Endocr Dev 2005;8:54-66.

53. Stikkelbroeck NM, Beerendonk CC, Willemsen WN, Schreuder-Bais CA, Feitz WF, Rieu PN. The long term outcome of feminizing genital surgery for congenital adrenal hyperplasia: anatomical, functional and cosmetic outcomes, psychosexual development, and satisfaction in adult female patients. J Pediatr Adolesc Gynecol 2003;16:289-296.

54. Gastaud F, Bouvattier C, Duranteau L, Brauner R, Thibaud E, Kutten F, Bougnères P. Impaired sexual and reproductive outcomes in women with classical forms of congenital adrenal hyperplasia. J Clin Endocrinol Metab 2007; 92:1391-1396.

55. Garner PR. Congenital adrenal hyperplasia in pregnancy. Semin Perinatol 1998; 22:446-546.

56. Amadori P. Reduced need of glucocorticoid therapy in a woman with congenital adrenal hyperplasia due to 21-hydroxylase deficiency during pregnancy. J Endocrionl Invest 2006; 29:848-850.

57. Witchel SF, Nayak S, Suda-Hartman M, Lee PA. Newborn screening for 21-hydroxylase deficiency: Results of CYP21 molecular genetic analysis. J Pediatr 1997; 131:328–331.

58. LWPES/ESPE CAH Working Group. Consensus statement on 21-hydroxylase deficiency from The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology. J Clin Endocrinol Metab 2002; 87:4048–4053.

59. Demirel F, Kara O, Tepe D, Esen I. Bone mineral density and vitamin D status in children and adolescents with congenital adrenal hyperplasia. Turk J Med Sci 2014; 44:109-114.

60. El-Maouche D, Collier S, Prasad M, Reynolds JC, Merke DP. Cortical bone mineral density in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol (Oxf) 2015;82:330-337.

61. Falhammar H, Filipsson H, Holmdahl G, Janson PO, Nordenskjöld A, Hagenfeldt K, Thorén M. Fractures and bone mineral density in adult women with 21-hydroxylase deficiency. J Clin Endocrinol Metab 2007;92:4643-4649.

62. Falhammar H, Filipsson Nyström H, Wedell A, Brismar K, Thorén M. Bone mineral density, bone markers, and fractures in adult males with congenital adrenal hyperplasia. Eur J Endocrinol 2013;168:331-341.

63. Romanowska H, Krzywińska-Zdeb E, Gieżewska M, Kotkowiak L, Safranow K, Horodnicka-Józwa A, Petriczko E, Krupa B, Walczak M. Estimation of influence of congenital-adrenal hyperplasia treatment on bone mineralisation evaluated with densitometry. Pediatr Endocrinol Diabetes Metab 2012;18:21-26.

64. Arisaka O, Hoshi M, Kanazawa S, Numata M, Nakajima D, Kanno S, Negishi M, Nishikura K, Nitta A, Imataka M, Kuribayashi T, Kano K. Preliminary report: effect of adrenal androgen and estrogen on bone maturation and bone mineral density. Metabolism 2001;50:377-379.

65. Findling JW, Raff H. Cushing's Syndrome: important issues in diagnosis and management. J Clin Endocrinol Metab 2006;91:3746-3753.

66. Labeur M, Theodoropoulou M, Sievers C. New aspects in the diagnosis and treatment of Cushing disease. Front Horm Res 2006;35:169-178.

67. Trainer PJ. Corticosteroids and pregnancy. Semin Reprod Med 2002;20:375-380.

68. Kamoun M, Mnif MF, Charfi N, Kacem FH, Naceur BB, Mnif F, Dammak M, Rekik N, Abid M. Adrenal diseases during pregnancy: pathophysiology, diagnosis and management strategies. Am J Med Sci 2014;347:64-73.

69. Kaltsas G, Makras P. Skeletal diseases in Cushing's syndrome: osteoporosis versus arthropathy. Neuroendocrinology 2010; 92:60-64.

70. Chiodini I, Morelli V, Masserini B, Salcuni AS, Eller-Vainicher C, Viti R, Coletti F, Guglielmi G, Battista C, Carnevale V, Iorio L, Beck-Peccoz P, Arosio M, Ambrosi B, Scillitani A. Bone mineral density, prevalence of vertebral fractures, and bone quality in patients with adrenal incidentalomas with and without subclinical hypercortisolism: an Italian multicenter study. J Clin Endocrinol Metab 2009; 94:3207-3214.

71. Chiodini I, Viti R, Coletti F, Guglielmi G, Battista C, Ermetici F, Morelli V, Salcuni A, Carnevale V, Urbano F, Muscarella S, Ambrosi B, Arosio M, Beck-Peccoz P, Scillitani A. Eugonadal male patients with adrenal incidentalomas and subclinical hypercortisolism have increased rate of vertebral fractures. Clin Endocrinol (Oxf) 2009; 70:208-213.

72. Minetto M, Reimondo G, Osella G, Ventura M, Angeli A, Terzolo M. Bone loss is more severe in primary adrenal than in pituitary-dependent Cushing's syndrome. Osteoporos Int 2004;15:855-861.

73. Ohmori N, Nomura K, Ohmori K, Kato Y, Itoh T, Takano K. Osteoporosis is more prevalent in adrenal than in pituitary Cushing's syndrome. Endocr J 2003;50:1-7.

74. Tauchmanovà L, Pivonello R, Di Somma C, Rossi R, De Martino MC, Camera L, Klain M, Salvatore M, Lombardi G, Colao A. Bone demineralization and vertebral fractures in endogenous cortisol excess: role of disease etiology and gonadal status. J Clin Endocrinol Metab 2006;91:1779-1784.

75. Trementino L, Appolloni G, Ceccoli L, Marcelli G, Concettoni C, Boscaro M, Arnaldi G. Bone complications in patients with Cushing's syndrome: looking for clinical, biochemical, and genetic determinants. Osteoporos Int 2014; 25:913-921.

76. Dos Santos CV, Vieira Neto L, Madeira M, Alves Coelho MC, de Mendonça LM, Paranhos-Neto FP, Lima IC, Gadelha MR, Farias ML. Bone density and microarchitecture in endogenous hypercortisolism. Clin Endocrinol (Oxf) 2015 [In Press].

77. Majumdar A, Mangal NS. Hyperprolactinemia. J Hum Reprod Sci 2013;6:168-75.

78. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA. Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:273-288.

79. Bolanowski M, Halupczok J, Jawiarczyk-Przybyłowska A. Pituitary disorders and osteoporosis. Int J Endocrinol 2015; 2015:206853.

80. Zadrozna-Sliwka B, Bolanowski M, Kałuzny M, Syrycka J. Bone mineral density and bone turnover in hyperprolactinaemia of various origins. Endokrynol Pol 2007; 58:116-122.

81. Mazziotti G, Porcelli T, Mormando M, De Menis E, Bianchi A, Mejia C, Mancini T, De Marinis L, Giustina A. Vertebral fractures in males with prolactinoma. Endocrine 2011;39:288-293.

82. Mazziotti G, Mancini T, Mormando M, De Menis E, Bianchi A, Doga M, Porcelli T, Vescovi PP, De Marinis L, Giustina A. High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas. Pituitary 2011; 14:299-306.

83. Carmina E, Rosato F, Jannì A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab 2006;91:2–6.

84. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, Shapiro J, Montori VM, Swiglo BA. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2008;93:1105–1120.

85. Castelo-Branco C, Gómez O, Pons F, Martinez de Osaba MJ, Balasch J, Antonio Vanrell J. Secreting ovarian tumors may protect women from osteoporosis. Gynecol Oncol 2003; 88:149-152.