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Influence of androgen levels on conception probability in patients undergoing fertility treatment: a retrospective cohort study

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Abstract

Purpose Primary and secondary sterility have become an issue of increasing importance due to demographic and social changes in society. Data regarding the association between female androgen levels and the probability of successful conception after fertility treatment are sparse and contradictive. This study was designed to assess this clinical question.

Methods In this retrospective single-center cohort study concentrations of androgens androstenedione, dehydroepiandrosteronsulfat (DHEAS) and testosterone (ng/ml) were investigated in the serum of patients presenting for sterility at the department of reproductive medicine of Saarland University hospital Homburg between January 2015 and December 2017. Androgen levels were correlated with reproductive outcomes. Statistical analysis was performed with the aid of SPSS version 24. Significance for conception rates in dependence of androgen concentration was assessed using Kruskal–Wallis test (significance was estimated with $p < 0.05$).

Results The laboratory values of a total of 301 patients were examined (64% primary, 36% secondary sterility). Median age at first visit at the fertility department was 32.7 years (range 20–47 years). 64 pregnancies were observed during the study period (conception rate 21.3%). 23 out of 301 patients (7.6%) suffered from hypoandrogenaemia, 248 (82.4%) had normal androgen levels and 30 (10%) showed hyperandrogenaemia ($p = 0.25$). Regarding patients in whom fertility treatment was successful 3 (4.7%) showed hypoandrogenaemia, 54 (84.4%) were normoandrogenaemic and 7 (10.9%) had hyperandrogenaemia ($p = 0.40$ Kruskal–Wallis test).

Conclusions We found no association between female androgen levels and sterility and reproductive outcomes.

Keywords Sterility · Fertility treatment · Conception rates · Hyperandrogenaemia · Hypoandrogenaemia

Purpose

Sterility is becoming an increasing issue, with estimated every seventh couple experiencing an unfulfilled desire to have children for more than a year [1].

The three main reasons for sterility are disorders of ovarian function, anatomical causes, as pathological tubal patency, or diminished motility of the tubes and andrological subfertility [2].

Around 30% of all infertile women have anovulatory cycles. Mostly, this is attributed to polycystic ovaries (PCOS). Features are high androgen levels, oligo- amenorrhea and enlarged ovaries > 34 mm with at least 10 peripheral antral follicles < 10 mm [3]. The relationship between PCOS and sterility has already been clearly proven. Data regarding the connection between female androgen levels and sterility, as well as conception rates after fertility treatment in these patients are sparse and rather contradictive [4].

Some authors found a negative correlation between hyper- and hypoandrogenaemia and conception rates [5], implying altered androgen levels to be a risk factor for sterility. Other studies showed no association between both factors [6]. This

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Table 1 Laboratory reference values of investigated androgens

Androgen	Reference range (ng/ml)
Testosterone	0.08–0.48
Androstenedione	0.3–3.3
Dehydroepiandrosterone sulfate	350–4300

study was designed to assess whether there is a correlation between androgen concentrations and sterility and conception rates in women undergoing fertility treatment.

Methods

In this retrospective single center cohort study we included all patients presenting for primary or secondary sterility at the department of reproductive medicine at the Saarland University hospital Homburg between January 2015 and December 2017. Patients were followed for one year regarding fertility outcomes. Serum concentrations of androgens (androstenedione, dehydroepiandrosteronsulfat (DHEAS), testosterone (ng/ml)) were analyzed on the 2nd–5th day of the menstrual cycle. Hypo- and hyperandrogenaemia were defined upon laboratory standards shown in Table 1. Hypoandrogenaemia was defined as a decreased serum level of at least androstenedione, DHEAS and/or testosterone, hyperandrogenaemia as an elevation in at least one of the serum androgens. Women with normoandrogenaemia had all three serum androgens within the reference area which can be seen in Table 1.

Patients' characteristics, fertility treatment and outcome data were collected from medical charts. Exclusion criteria were missing data on study values or missing follow-up data.

For further analysis the cohort was divided into two subgroups, one consisting of patients in whom fertility treatment was successful and one with persistent sterility. Median androgen levels were calculated and compared between the two groups. For statistical analysis we applied the Kruskal–Wallis test for three independent samples (hyperandrogenaemia, normoandrogenaemia, and hypoandrogenaemia). Level of significance was defined as $p < 0.05$. Statistical analysis was performed with SPSS version 24 (IBM, Armonk, New York, USA). Since we retrospectively collected anonymous clinical parameters for this study, no consent of patients` participation was needed according to the institutional review board.

Results

301 out of 324 patients presenting with sterility were included in the final analysis. 41 patients were excluded because of missing follow-up data, seven due to incomplete study data. 193 (64%) of the finally analyzed patients were diagnosed with primary sterility, 108 (36%) with secondary. The median age at first visit was 32.7 years (range 20–47 years). 64 conceptions were conceived in the reviewed period between January 2015 and December 2017, which corresponds to a cumulative pregnancy rate of 21.3%. Table 2 shows the fertility treatment techniques used in women with successful conception after fertility therapy.

Patients became pregnant within a median latency of 12.8 months (range 1–78 months) after visiting our fertility clinic for the first time. 53 out of 301 patients (17.6%) had alterations of androgen levels. A total of 23 (7.6%) women showed hypoandrogenaemia, 30 (10%) women showed laboratory signs of hyperandrogenaemia. Only 3 (4.7%) of the women with successful conception showed hypoandrogenaemia, 54 (84.4%) had normal androgen levels, and 7 (10.9%) suffered from hyperandrogenaemia ($p = 0.25$). The androgen levels were not altered in 248 (82.4%) women. In women in whom conception was not achieved 20 (8.4%) had a hypoandrogenaemia, 194 (81.9%) had normal androgen blood concentrations and 23 (9.7%) had a hyperandrogenaemia (Table 3). Pathologically altered androgen concentrations were not significantly different between patients with conception and those who did not conceive ($p = 0.40$). Figure 1 shows the proportions of low, unaffected and increased androgen levels in patients with fertility problems within the basic hormone diagnostics regarding probability of becoming pregnant. Table 4 shows the correlation between levels of androgen and conception rate in patients with sterility.

Table 2 Fertility treatment techniques used in women with successful conception after fertility therapy ($n = 64$)

Number of conceptions *n* (%)	Fertility technique applied
13 (20.3)	Intercourse in a natural spontaneous cycle
11 (17.2)	Planned period of time in a stimulated cycle
4 (6.3)	Intrauterine insemination (IUI)
4 (6.3)	Stimulated intrauterine insemination
10 (15.6)	In vitro fertilization (IVF)
13 (20.3)	Intracytoplasmic sperm injection (ICSI)
9 (14.1)	Cryo cycle

Table 3 Conception rates in women with hypo-, hyper- and normoandrogenaemia ($n=301$)

	Hypoandrogenaemia $n=23$ (7.6%)	Hyperandrogenaemia $n=30$ (10%)	Normoandrogenaemia $n=248$ (82.4%)
Conception			
Yes	3 (1.0)	7 (2.3)	54 (17.9)
No	20 (6.6)	23 (7.6)	194 (64.5)

Discussion

Elevated androgen levels as part of the PCO syndrome are known risk factors for sterility [5]. Until today, the exact pathomechanism of the PCO has not been detected. Nowadays we know about an increased pulsatile release of luteinizing hormone (LH), an insufficiency of the aromatase in the peripheral fat tissue and hyperinsulinaemia which supports hyperandrogenaemia by a reduced synthesis of sex hormone binding globulin (SHBG) [7]. By contrast, little is known about low androgen levels in women and their impact on reproduction. In 2015, Gleicher et al. [8] published that female androgen levels are correlated with the risk of sterility, but not with an aneuploidy. Consequently, low androgen levels might be a risk factor for sterility [9]. Our data showed no correlation between low androgen levels and conception rates.

Interestingly, androgen substitution is recommended by several authors before the use of assisted reproductive technologies to improve fertility treatment outcomes [10]. For some years—even though experimental—androgens, mostly DHEA, have been applied to women with limited ovary reserve over a period of 2–3 months before starting hormonal stimulation treatment. This should stimulate follicles to grow and help to increase the amount of punctured eggs [10, 11]. In contrast, there are authors who do not recommend androgen substitution in women with fertility problems for lack of evidence [12]. Yeung et al. published a

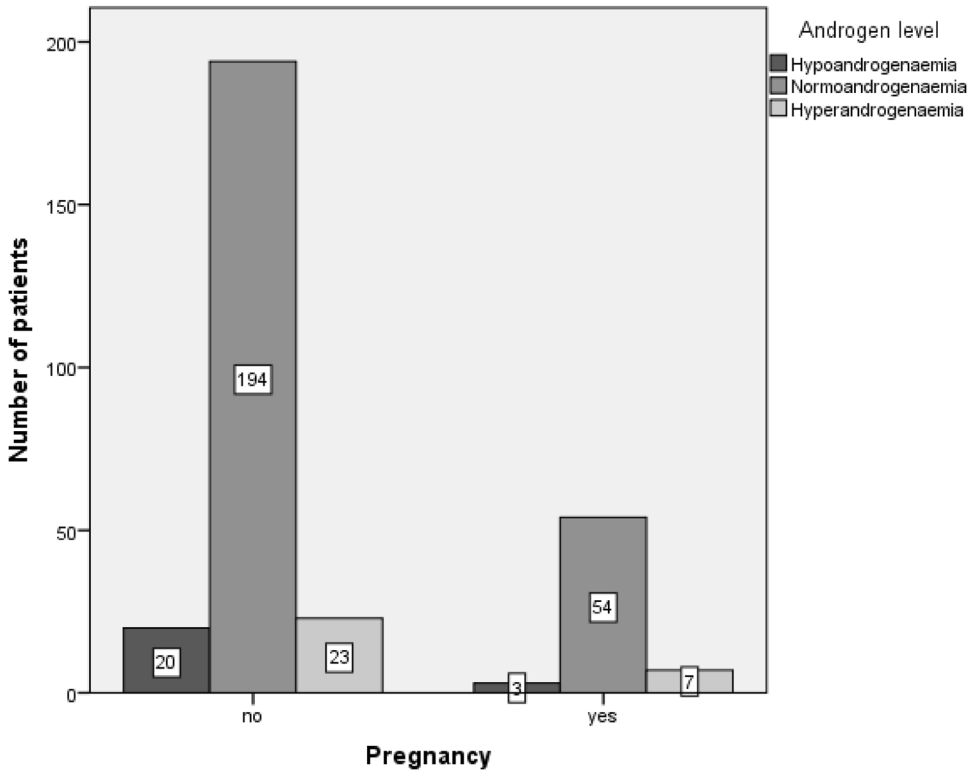

Fig. 1 Pregnancy probability depending on the level of androgen within basic hormone diagnostics, $n=301$

Table 4 Correlation between levels of androgen and pregnancy start in patients with sterility ($n=301$)

Level of androgen	Androstenedione (ng/ml)	DHEAS (ng/ml)	Testosterone (ng/ml)
Pregnancy	1.96 (0.7–6.3)	1738 (486–4420)	0.3 (0.02–0.69)
No pregnancy	1.8 (0.4–6.4)	1660 (60–4780)	0.28 (0.03–0.85)
Significance test (Kruskal–Wallis test)	$p=0.10$	$p=0.41$	$p=0.14$

small placebo-controlled randomized study with 16 women with poor ovarian response upon DHEA supplementation during assisted reproductive treatment. This did not affect conception rates [12, 13].

Triantafyllidou et al. state that after poor response to an ovarian stimulation treatment due to limited ovarian reserve, the steroid synthesis and the follicle recruitment might be increased by giving DHEA. This means the number of maturing pre-antral follicles and possibly also the number of mature follicles could be increased [11]. In 2015, Nagels et al. published a systematic review analyzing 17 randomized studies with a total of 1496 patients receiving DHEA as part of assisted reproductive treatment. Live-born and continuous pregnancy rates (26% versus 12%) could be increased by up to two times after DHEA supplementation [13].

However, conclusive data of prospective randomized controlled clinical trials do not exist in the literature. Only limited data are available regarding the benefit of androgen treatment in women with fertility problems. For this reason, the American Endocrine Society does not recommend androgen substitution as part of reproductive treatment [14]. Moreover there is a lack of a standardized definition of female androgen deficiency syndrome [15]. Every laboratory possesses its own reference values and the assessment of hyper- or hypoandrogenaemia can vary inter-individually.

According to a review concerning this issue results published by Nagels et al. there seems to be a tendency towards a disadvantage of women with hypoandrogenaemia regarding conception rates. In this point of view, data of our study might support the hypothesis that different serum levels of androgens are accompanied with different probabilities of conception with the tendency of a lower conception rate in cases of hypoandrogenaemia. However, our study has its limitations. First of all, the sample size of 301 patients is small and statistical conclusions have to be drawn and interpreted with caution. Another limitation lies in the study design. With including only patients from one department—who were observed throughout a limited period of 12 months—the number of patients and the follow-up are limited. Moreover, there is no overview about the complete clinical course of pregnancy as women left the department after the sonographic detection of embryonal heartbeat. Moreover our study does not differentiate whether enhanced female androgen levels in the serum originate from other sources such as PCOS, or an intake of androgens containing medicine or from a tumor which produces androgens. All these factors not included could have a significant impact on the conception probability. Low levels of androgen might be linked to the perimenopausal hormone status. We did neither determine SHBG nor free androgen index.

At the same time, potential risks due to androgen application have to be considered by the therapists and potential side effects of androgen treatment have to be outweighed against the possible benefits. A hyperandrogenaemia, particularly elevated testosterone, is accompanied by an increased intima-media thickness (IMT) of blood vessels. This is regarded as a cardiovascular risk factor [16]. Dehydroepiandrosterone is said to influence the testosterone level in the perimenopause [17, 18]. Further studies are required, especially the evaluation of therapeutic options for sterile women with poor ovarian response [19, 20].

Finally, sterility is a sensitive and multifactorial clinical problem and assignment to one risk factor might ignore other interfering factors such as post adnexitis status or unhealthy lifestyle. Since it is a retrospective study there are several confounders influencing each other. We are sensible of our study's methodological weakness. Nevertheless, it has to be emphasized that several other studies examining the relationship between androgen levels and sterility also evaluated small patient populations [13]. In the future, further, prospective well-designed studies are necessary to answer this clinical question.

Conclusions

In our retrospective cohort study, we found no significant association between androgen alterations and sterility and conceptions rates in women undergoing fertility treatment.

Author contributions SF: preparation of the manuscript, data analysis, and literature review. PS: layout. LS: statistics. RMS: statistics. II: figure. CS: tables. MK: literatur review. FT: statistics and development of the concept. EFS: counseling and proof of content. JCR: preparation of the manuscript, data analysis, and literature review.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval The study was conducted in concordance to the ethical standards of the institution.

Informed consent As this was a retrospective study including only laboratory parameters no informed consent was obtained.

References

1. Sexty RE, Hamadneh J, Rösner S et al (2016) Cross-cultural comparison of fertility specific quality of life in German, Hungarian and Jordanian couples attending a fertility center. Health Qual Life Outcomes 14:27
2. Diamond MP, Legro RS, Coutifaris C et al (2017) Sexual function in infertile women with polycystic ovary syndrome and unexplained infertility. Am J Obstet Gynecol 217(2):191

3. Norman RJ, Dewailly D, Legro RS, Hickey TE (2007) Seminar: polycystic ovary syndrome. Lancet 370:685–697
4. Hossein Rashidi B, Hormoz B, Shahrokh Theraninejad E, Shariat M, Mahdavi A (2009) Testosterone and dehydroepiandrosterone sulphate levels and IVF/ICSI results. Gynecol Endocrinol 25(3):194–198
5. Göretzlehner G, Lauritzen C (1990) Praktische Gynäkologie, 1st edn. de Gruyter, Berlin
6. Sunkara SK, Coomarasamy A (2011) Androgen pretreatment in poor responders undergoing controlled ovarian stimulation and in vitro fertilization treatment. Fertil Steril 95(8):e73–e74
7. Cunningham P (2017) Pathophysiology, diagnosis and treatment of polycystic ovary syndrome. Nurs Stand 31(39):44–51
8. Gleicher N, McCulloh DH, Kushnir VA et al (2015) Is there an androgen level threshold for aneuploidy risk in infertile women? Reprod Biol Endocrinol 6(13):38
9. Shirazi TN, Bossio JA, Puts DA, Chivers ML (2018) Menstrual cycle phase predicts women's hormonal responses to sexual stimuli. Horm Behav 103:45–53
10. Narkwichean A, Maalouf W, Campbell BK, Jayaprakasan K (2013) Efficacy of dehydroepiandrosterone to improve ovarian response in women with diminished ovarian reserve: a meta-analysis. Reprod Biol Endocrinol 11:44
11. Triantafyllidou O, Sigalos G, Vlahos N (2017) Dehydroepiandrosterone (DHEA) supplementation and IVF outcome in poor responders. Hum Fertil (Camb) 20(2):80–87
12. Kim CH (2013) Androgen supplementation in IVF. Minerva Ginecol 65(5):497–504
13. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B (2015) Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev 26(11):CD009749
14. Qin JC, Fan L, Qin AP (2016) The effect of dehydroepiandrosterone (DHEA) supplementation on women with diminished ovarian reserve (DOR) in IVF cycle: Evidence from a meta-analysis. J Gynecol Obstet Biol Reprod (Paris) 46(1):1–7
15. Wierman ME, Arlt W, Basson R (2014) Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 99(10):3489–3510
16. Yilmaz SA, Kebapcilar A, Koplay M, Kerimoglu OS, Pekin AT, Gencoglu B, Dogan NU, Celik C (2015) Association of clinical androgen excess with radial artery intima media thickness in women with polycystic ovary syndrome. Gynecol Endocrinol 31(6):477–482
17. Lasley BL, Santoro N, Randolf JF, Gold EB, Crawford S, Weiss G, McConnell DS, Sowers MF (2002) The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. J Clin Endocrinol Metab. 87(8):3760–3767
18. Yeung TW, Chai J, Li RH, Lee VC, Ho PC, Ng EH (2014) A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and in vitro fertilization outcomes in poor responders. Fertil Steril 102(1):108–115
19. Ubaldi FM, Rienzi L, Ferrero S, Baroni E, Sapienza F, Cobellis L, Greco E (2005) Management of poor responders in IVF. Reprod Biomed Online 10(2):235–246
20. Surrey ES, Schoolcraft WB (2000) Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. Fertil Steril 73(4):667–676