A CASE OF TESTOSTERONE SUPPLEMENTATION IMPROVING IVF OUTCOME IN A "LEAN" PCOS WOMAN WITH HISTORY OF POOR EMBRYONIC DEVELOPMENT AND FAILED IVF CYCLE: A CASE REPORT AND LITERATURE REVIEW

Rumana Rahman[1,*], Timothy Bracewell-Milnes[2], and Dimitrios Nikolaou[3]

[1]Assisted Conception Unit, Chelsea and Westminster Hospital, 369 Fulham Road, London, UK

[2]Division of Surgery and Cancer, Institute of Developmental Reproductive & Developmental Biology, Imperial College London, Chelsea and Westminster Hospital Campus, 369 Fulham Road, London, UK

[3]Chelsea and Westminster Hospital, 369 Fulham Road, London, UK.

Correspondence E-mail: rumana.rahman@doctors.org.uk

INTRODUCTION

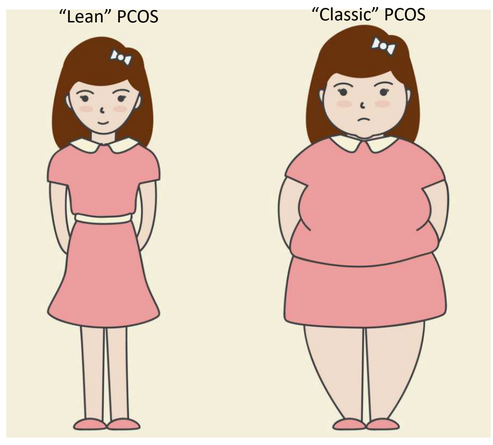
Polycystic ovarian syndrome (PCOS) is a common endocrine and metabolic disorder in women of reproductive age. PCOS women can be classified into "classic" and "lean" groups. The "classic" phenotype represents over 50% of PCOS women. The rest exhibit a "lean" phenotype, representing non-obese women with low to normal body mass index and lacking many of the typical characteristics of "classic" PCOS. Hyperandrogenism is a key feature in most PCOS patients. However, raised serum androgen levels and ovarian dysfunction seem to resolve with advancing age. In the "lean" group, testosterone level declines disproportionately faster compared to the Anti-Mullerian hormone (AMH) level, resulting in relative hypoandrogenism with ageing. In contrast, "classic" PCOS women show a synchronous decline in AMH and testosterone levels with advancing age, thereby avoiding the issue of hypoandrogenism. It is well established that androgens play a crucial role in promoting normal folliculogenesis, which in turn affects oocyte yield and oocyte/embryo quality during in-vitro fertilisation (IVF). Hypoandrogenism with advancing age in "lean" PCOS group can, therefore, have a detrimental effect on IVF outcomes.

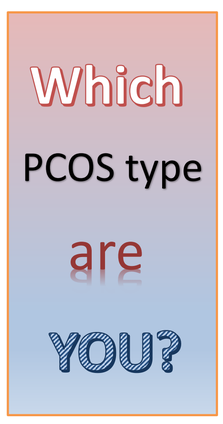
RESULTS

Case report: This case report describes a successful outcome of IVF in a woman with "lean" PCOS following testosterone supplementation prior to IVF. A 34-year old nulliparous woman presented with her 34-year old male partner to our general fertility clinic at the Chelsea and Westminster Hospital with a 2- year history of primary subfertility. The partner had obstructive azoospermia and had to undergo microsurgical testicular sperm extraction (microTESE). Upon thawing the extracted sperm, it was found to be motile and did not require stimulation. However, unfortunately out of the 4 eggs that were injected using the sperm, none fertilised. The first cycle of ovarian stimulation yielded a below average number of oocytes and none of them fertilised with intracytoplasmic sperm injection (ICSI), despite the sperm being of adequate quality, therefore, suggesting a possible issue with oocyte quality. The patient's testosterone level was found to be below normal range and hence, she received testosterone supplementation for 3 months prior to the next ICSI cycle. Interestingly, in the cycle following testosterone pre-treatment, there was successful fertilisation using the same sperm sample and this resulted in two good quality embryos. The embryo transfer was successful, and she is currently 29 weeks pregnant.
Discussion: In the above case the first cycle of IVF yielded 7 oocytes but none of them fertilised. Firstly, the number of oocytes retrieved following ovarian stimulation was below the expected average number, in view of her high AMH (35pmol/L). Additionally, failure of the sperm in fertilising any of the eggs was even more surprising. Even though the sperm was surgically extracted and frozen, upon thawing the sample showed normal characteristics and was perfectly suitable for ICSI. Therefore, it can only be assumed that the failure in fertilisation was most likely due to poor egg quality. This group of PCOS women start off with excess androgen levels. With advancing age, androgen levels can decline dramatically below a certain threshold level that is crucial for normal ovarian function and for producing good quality embryos. However, previous studies have shown that androgen supplementation to bring the androgen levels back to the normal physiological range in these patients prior to IVF treatment can actually be very effective in improving follicular development, embryo quality and pregnancy rates. This case report demonstrates how "lean" PCOS women are more resistant to fertility treatment and more challenging to treat when compared with "classic" PCOS group. It also portrays the fact that the "lean" PCOS phenotype often develop hypoestrogenism in their late 20s to mid 30s. Following testosterone supplementation in the second IVF cycle, there was a significant improvement in fertilisation rate and embryo quality thus indicating a positive effect of testosterone on ovarian function; a theory that has been proposed by several study groups in the past.

Rotterdam	NIH/NICHD	Androgen Excess Society
PCOS is considered a diagnosis of exclusion.	PCOS is considered a diagnosis of exclusion.	PCOS is considered a diagnosis of exclusion.
Diagnosis requires two of:	Diagnosis requires all of:	Diagnosis requires all of:
Hyperandrogenism	Hyperandrogenism	Hyperandrogenism
Polycystic ovaries	Menstrual disturbance	Polycystic ovaries and/or 'ovarian dysfunction'
Anovulation/oligo-ovulation		

Table 1: Definition of PCOS according to the diagnostic criteria set by three different groups
(Toosy, S., Sodi, R., & Pappachan, J. M. (2018). Lean polycystic ovary syndrome (PCOS): An evidence-based practical approach. *Journal of Diabetes and Metabolic Disorders, 17*(2), 277-285. doi:10.1007/s40200-018-0371-5)





Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
PCOS features	HA/OD/PCOM	HA/OD	HA/PCOM	OD/PCOM
HA	+	+	+	–
OD	+	+	–	+
PCOM	+	–	+	+
NIH 1990 criteria	X	X		
Rotterdam 2003 criteria	X	X	X	X
AE-PCOS 2006 criteria	X	X	X	

Note: AE-PCOS = Androgen Excess & PCOS Society; HA = hyperandrogenism; NIH = National Institutes of Health; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology.

Table 2: Classification of PCOS phenotypes
(Lizneva, D., Suturina, L., Walker, W., Brakta, S., Gavrilova-Jordan, L., & Azziz, R. (2016). Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertility and Sterility, 106*(1), 6-15. doi:10.1016/j.fertnstert.2016.05.003)

CONCLUSION

This case report emphasises how the "classic" and "lean" PCOS groups differ widely in the pathophysiology, phenotype and fertility treatment outcome. Therefore, clinicians should tailor the treatment according to the group of PCOS that they are dealing with. It is also important to remember that the rate of decline of androgen levels is very different in the two groups. Since, normal androgen level is a key factor in determining ovarian function and eventually fertility outcome, it would be beneficial to routinely check androgen levels in PCOS patients, especially the "lean" PCOS group. Normalising the androgen levels can help to improve IVF outcome in "lean" PCOS patients with hypoandrogenism. Therefore, helping to avoid fertility treatment failure and the significant emotional and psychological burden on the patient that comes with a failed IVF cycle.

REFERENCES

Bailey, A. P., Hawkins, L. K., Missmer, S. A., Correia, K. F., & Yanushpolsky, E. H. (2014). Effect of body mass index on in vitro fertilization outcomes in women with polycystic ovary syndrome. *American Journal of Obstetrics and Gynecology, 211*(2), 163.e1-163.e6. doi:10.1016/j.ajog.2014.03.035

Brown, Z. A., Louwers, Y. V., Fong, S. L., Valkenburg, O., Birnie, E., de Jong, F. H., et al. (2011). The phenotype of polycystic ovary syndrome ameliorates with aging. *Fertility and Sterility, 96*(5), 1259-1265. doi:10.1016/j.fertnstert.2011.09.002

Escobar-Morreale, H. F. (2018). Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. Nature *Reviews. Endocrinology, 14*(5), 270-284. doi:10.1038/nrendo.2018.24

Gleicher, N., Gleicher, N., Kushnir, V., Kushnir, V., Darmon, S., Darmon, S., et al. (2018). Suspected ontogeny of a recently described hypo-androgenic PCOS-like phenotype with advancing age. *Endocrine, 59*(3), 661-676. doi:10.1007/s12020-017-1498-8

Gleicher, N., Kim, A., Weghofer, A., Kushnir, V. A., Shohat-Tal, A., Lazzaroni, E., et al. (2013). Hypoandrogenism in association with diminished functional ovarian reserve. *Human Reproduction, 28*(4), 1084-1091. doi:10.1093/humrep/det033

Gleicher, N., Kushnir, V. A., Darmon, S. K., Wang, Q., Zhang, L., Albertini, D. F., et al. (2017). New PCOS-like phenotype in older infertile women of likely autoimmune adrenal aetiology with high AMH but low androgens. *Journal of Steroid Biochemistry and Molecular Biology, 167*, 144-152. doi:10.1016/j.jsbmb.2016.12.004

Goldrat, O., & Delbaere, A. (2018). PCOS: Update and diagnostic approach. *Clinical Biochemistry, 62*, 24-31. doi:10.1016/j.clinbiochem.2018.09.001

Goyal, M., & Dawood, A. S. (2017). Debates regarding lean patients with polycystic ovary syndrome: A narrative review. *Journal of Human Reproductive Sciences, 10*(3), 154-161. doi:10.4103/jhrs.JHRS_77_17

Kushnir, V. A., Halevy, N., Barad, D. H., Albertini, D. F., & Gleicher, N. (2015). Relative importance of AMH and androgens changes with aging among non-obese women with polycystic ovary syndrome. *Journal of Ovarian Research, 8*(1), 45. doi:10.1186/s13048-015-0175-x

Lizneva, D., Suturina, L., Walker, W., Brakta, S., Gavrilova-Jordan, L., & Azziz, R. (2016). Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertility and Sterility, 106*(1), 6-15. doi:10.1016/j.fertnstert.2016.05.003

Prizant, H., Gleicher, N., & Sen, A. (2014). Androgen actions in the ovary: Balance is key. *Journal of Endocrinology, 222*(3), R141-R151. doi:10.1530/JOE-14-0296

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS).(2004). *Human Reproduction (Oxford), 19*(1), 41-47. doi:10.1093/humrep/deh098

Toosy, S., Sodi, R., & Pappachan, J. M. (2018). Lean polycystic ovary syndrome (PCOS): An evidence-based practical approach. *Journal of Diabetes and Metabolic Disorders, 17*(2), 277-285. doi:10.1007/s40200-018-0371-5

ACKNOWLEDGEMENTS

We would like to thank all our colleagues at the Assisted Conception Unit at Chelsea and Westminster Hospital, London.