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# **Comorbid polycystic ovarian syndrome in idiopathic intracranial hypertension**

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# **Comorbid polycystic ovarian syndrome in idiopathic intracranial hypertension**

The prevalence of polycystic ovarian syndrome (PCOS) and idiopathic intracranial hypertension (IIH) occurring together has long been debated. Historically, there is a wide range of reported occurrence of both conditions being between 15-64%. Both conditions share a common phenotype. The awareness that in a new large data study that there is a 1.5-fold increased prevalence of diagnosed PCOS in participants with IIH as compared to the controls is important. Assessment for the potential of comorbid PCOS in women with IIH as this may enable optimisation of weight and fertility management.

Keywords: Polycystic ovarian syndrome, prevalence, pseudotumour cerebri.

## **Dear Editor,**

Idiopathic Intracranial Hypertension (IIH) typically affects reproductive aged women with obesity.[1, 2] The manifestations of this disease are increasingly being identified beyond the traditional known headache and visual symptoms.[3, 4] The prevalence of polycystic ovarian syndrome (PCOS) and idiopathic intracranial hypertension (IIH) occurring together has long been debated. Case series suggest co-existence of the two conditions in 15-64% of women with IIH.[5-8] Both are phenotypically similar with systemic metabolic dysfunction,[9-13], truncal adiposity,[13-15] insulin resistance,[9, 12] reduced fertility[16-18], gestational complications[16, 19] and an increased cardiovascular risk.[20] They are hyperandrogenic disorders but with distinct hormonal signatures.[21] The prevalence of comorbid PCOS in IIH compared to age and BMI matched controls has not been previously assessed.

In a recent population based longitudinal cohort study of >50,000 women that evaluated medication prescribing habits in women with IIH (n=3411) and population controls (n=33,495) was recently published in Neurology.[22] It reported that a higher

proportion in the IIH group had PCOS (7.4%) compared to matched population controls (4.9%) at study entry,[22] corresponding to a 1.5-fold increased prevalence of diagnosed PCOS in participants with IIH compared to the controls. This is similar to Avisar et al, who showed a 1.8-fold increase of 15.5% PCOS in IIH versus 8.9% in their general population.[5]

The 1.5 fold increased prevalence of comorbid PCOS in IIH is an important finding and supports this more recent literature[5] and refutes the earlier overestimations reported.[6-8] This is important as it may influence weight and fertility management, e.g. metformin aids weight loss when both diseases are present.[6]

Weight gain is a key precipitant in the development of IIH [23], and a recent randomised control trial has shown the benefit of weight loss in lowering raised intracranial pressure to inducing remission of the condition.[24] Weight loss targets of 5-10% are often reported and is based to the general obesity literature[25] but in clinical practice are variable and often higher amounts are required[24, 26, 27] and can be even more challenging in certain scenarios including pregnancy.[28] Weight loss in PCOS has been achieved through lifestyle management,[29] medical management, i.e. Orlistat[30-32], Metformin[31, 32] and GLP-1 receptor agonists[33], and bariatric surgery especially in those unresponsive to lifestyle-medical treatment.[26] Medical management of comorbid PCOS may aid the weight loss required for IIH disease control. Metformin has been shown to aid weight loss in IIH where comorbid PCOS is present[6] although this is not part of routine clinical care and not currently a recommendation within IIH management.[3]

Additional ovulatory benefits have been shown for weight loss prior to pharmacotherapy use for infertility.[34, 35] Where fertility issues are present the use of

medications, i.e. clomiphene citrate, letrozole and metformin, are recommended[17] and could be beneficial in this illustrated combined cohort.

We recommend assessing for the potential of comorbid PCOS in IIH patients as this may enable optimisation of weight and fertility management options. What is yet to be determined is whether the combination of these disorders confers additional risks to vision, headache or cardiovascular morbidity.

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Declaration of Interest:

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## References

1. Mollan, S.P., et al., *New horizons for idiopathic intracranial hypertension: advances and challenges*. Br Med Bull, 2020. **136**(1): p. 118-126.
2. Thaller, M., et al., *The Idiopathic Intracranial Hypertension prospective cohort study: Evaluation of prognostic factors and outcomes*. Journal of Neurology, 2022.
3. Mollan, S.P., et al., *Idiopathic intracranial hypertension: consensus guidelines on management*. J Neurol Neurosurg Psychiatry, 2018. **89**(10): p. 1088-1100.
4. Mollan, S.P., et al., *Intracranial pressure directly predicts headache morbidity in idiopathic intracranial hypertension*. J Headache Pain, 2021. **22**(1): p. 118.
5. Avisar, I., et al., *The prevalence of polycystic ovary syndrome in women with idiopathic intracranial hypertension*. Scientifica (Cairo), 2012. **2012**: p. 708042.
6. Glueck, C.J., et al., *Changes in weight, papilledema, headache, visual field, and life status in response to diet and metformin in women with idiopathic intracranial hypertension with and without concurrent polycystic ovary syndrome or hyperinsulinemia*. Transl Res, 2006. **148**(5): p. 215-22.

7. Glueck, C.J., et al., *Idiopathic intracranial hypertension, polycystic-ovary syndrome, and thrombophilia*. J Lab Clin Med, 2005. **145**(2): p. 72-82.
8. Glueck, C.J., et al., *Idiopathic intracranial hypertension: associations with coagulation disorders and polycystic-ovary syndrome*. J Lab Clin Med, 2003. **142**(1): p. 35-45.
9. Westgate, C.S.J., et al., *Systemic and adipocyte transcriptional and metabolic dysregulation in Idiopathic Intracranial Hypertension*. JCI Insight, 2021. **6**(10): p. e145346.
10. Grech, O., et al., *Alterations in metabolic flux in migraine and the translational relevance*. J Headache Pain, 2022. **23**(1): p. 127.
11. Grech, O., et al., *Nuclear Magnetic Resonance Spectroscopy Metabolomics in Idiopathic Intracranial Hypertension to Identify Markers of Disease and Headache*. Neurology, 2022: p. 10.1212/WNL.000.
12. Kempegowda, P., et al., *Implicating androgen excess in propagating metabolic disease in polycystic ovary syndrome*. Ther Adv Endocrinol Metab, 2020. **11**: p. 2042018820934319.
13. O'Reilly, M.W., et al., *AKRIC3-Mediated Adipose Androgen Generation Drives Lipotoxicity in Women With Polycystic Ovary Syndrome*. J Clin Endocrinol Metab, 2017. **102**(9): p. 3327-3339.
14. Hornby, C., et al., *Metabolic Concepts in Idiopathic Intracranial Hypertension and Their Potential for Therapeutic Intervention*. J Neuroophthalmol, 2018. **38**(4): p. 522-530.
15. Hornby, C., et al., *Evaluating the Fat Distribution in Idiopathic Intracranial Hypertension Using Dual-Energy X-ray Absorptiometry Scanning*. Neuroophthalmology, 2018. **42**(2): p. 99-104.
16. Thaller, M., et al., *Idiopathic intracranial hypertension: evaluation of births and fertility through the hospital episode statistic dataset*. BJOG, 2022. **129**(12): p. 2019-2027.
17. Teede, H.J., et al., *Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome*. Clin Endocrinol (Oxf), 2018. **89**(3): p. 251-268.
18. Joham, A.E., et al., *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. **24**(4): p. 299-307.
19. Subramanian, A., et al., *Polycystic ovary syndrome and risk of adverse obstetric outcomes: a retrospective population-based matched cohort study in England*. BMC Medicine, 2022. **20**(1).
20. Adderley, N.J., et al., *Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom*. JAMA Neurol, 2019.
21. O'Reilly, M.W., et al., *A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics*. JCI Insight, 2019. **4**(6).
22. Adderley, N.J., et al., *Headache, Opiate Use, and Prescribing Trends in Women With Idiopathic Intracranial Hypertension: A Population-Based Matched Cohort Study*. Neurology, 2022.
23. Mollan, S.P., A.A. Tahrani, and A.J. Sinclair, *The Potentially Modifiable Risk Factor in Idiopathic Intracranial Hypertension: Body Weight*. Neurology: Clinical Practice, 2021: p. 10.1212/CPJ.0000000000001063.

24. Mollan, S.P., et al., *Effectiveness of Bariatric Surgery vs Community Weight Management Intervention for the Treatment of Idiopathic Intracranial Hypertension: A Randomized Clinical Trial*. JAMA Neurol, 2021. **78**(6): p. 678-686.
25. Jensen, M.D., et al., *2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society*. Circulation, 2014. **129**(25 Suppl 2): p. S102-38.
26. Glueck, C.J. and N. Goldenberg, *Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics*. Metabolism, 2019. **92**: p. 108-120.
27. Mollan, S.P., et al., *Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension*. Neurology, 2022: p. 10.1212/WNL.0000000000200839.
28. Thaller, M., et al., *Managing idiopathic intracranial hypertension in pregnancy: practical advice*. Practical Neurology, 2022: p. practneurol-2021-003152.
29. Lie Fong, S., A. Douma, and J. Verhaeghe, *Implementing the international evidence-based guideline of assessment and management of polycystic ovary syndrome (PCOS): how to achieve weight loss in overweight and obese women with PCOS?* J Gynecol Obstet Hum Reprod, 2021. **50**(6): p. 101894.
30. Graff, S.K., et al., *Effects of orlistat vs. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis*. International Journal of Clinical Practice, 2016. **70**(6): p. 450-461.
31. Cho, L.W., et al., *Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome*. Clin Endocrinol (Oxf), 2009. **70**(2): p. 233-7.
32. Ghandi, S., et al., *The effects of metformin or orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study*. Journal of Assisted Reproduction and Genetics, 2011. **28**(7): p. 591-596.
33. Cena, H., L. Chiovato, and R.E. Nappi, *Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists*. The Journal of Clinical Endocrinology & Metabolism, 2020. **105**(8): p. e2695-e2709.
34. Legro, R.S., et al., *Benefit of Delayed Fertility Therapy With Preconception Weight Loss Over Immediate Therapy in Obese Women With PCOS*. J Clin Endocrinol Metab, 2016. **101**(7): p. 2658-66.
35. Balen, A.H., et al., *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. **22**(6): p. 687-708.