**Cardiovascular Risks and Sympathovagal Imbalance In Polycystic Ovarian Syndrome**

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**Abstract:** Polycystic ovary syndrome (PCOS), the commonest cause of infertility, is a heterogeneous syndrome with a significant alteration in autonomic modulation in the form of increased adrenergic drive and a depressed vagal activity. The various co-morbidities associated with PCOS such as obesity, insulin resistance, dyslipidemia, hyperandrogenism and altered thyroid profile, are known to cause significant alteration in autonomic dysfunctions. Assessment of autonomic functions has proved to be a sensitive tool in diagnosing the early features of CV dysfunction in PCOS. When detected early, it enables an early intervention to yield a better cardiovascular health to these patients. The simplest approach of restoring the sympathovagal balance would be the life style modifications in the form of regular exercise and practice of yoga. Regular exercise decreases adiposity and improves the sensitivity of insulin in the peripheral tissues and yoga improves general cardiovascular health. Thus, these alternative therapies can supplement the medical therapy advocated to these patients and would lead to better outcome in both reproductive and cardiovascular health.

**Key words:** Cardiovascular dysfunctions, sympathovagal imbalance, PCOS

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**Introduction:** Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder seen in women of reproductive age group, affecting 5 to 10 % of the population1,2. PCOS has always been a topic of debate due to its diverse pathophysiologic mechanisms and the resultant heterogenous clinical manifestations1,2. In the recent few decades, PCOS has undergone a transition from merely being a benign reproductive endocrinopathy to a common infertility disorder, which has significant implications on cardiovascular health. Therefore, this review has been done to elaborate the cardiovascular implications of PCOS and the resultant autonomic dysfunction.

**Polycystic Ovary Syndrome :** Polycystic ovary syndrome is a complex chronic endocrine disorder of women in the reproductive age group which is classically characterized by three features i.e. oligovulation or anovulation, elevated levels of androgens and morphological changes in ovaries evident on ultrasound3. The first systematic description of PCOS was published by Irving Stein and Michael Leventhal, the American gynaecologists in the year 1935 and so PCOS is also designated as the Stein Leventhal syndrome4. PCOS was originally described by them in seven women as a combination of hirsutism, obesity, amenorrhea and enlarged bilateral polycystic ovaries (PCO)5. They also reported bilateral wedge resection of ovaries as a therapy for PCOS. They postulated that removing the thickened capsule of ovary would allow the follicles to reach the surface of the ovary and restore normal ovulation. Based on their observation, a primary ovarian defect was inferred and was referred to as polycystic ovarian disease. Subsequent studies revealed much more clinical and hormonal derangements and the term PCOS was introduced to depict the heterogeneity of the disorder5. Hyperandrogenism and insulin were linked as early as 1921 when French physicians, Achard and Thiers published their classic description of a bearded women with diabetes (diabetes des femmes a barbe)6. One of the milestone discoveries was the association of IR to PCOS, by Burghen et al in 19806. Further studies on this aspect have had significant therapeutic implications6.

**Diagnostic Criteria of PCOS:** Historically the combination of androgen excess, anovulation and obesity has been considered as the hallmark of PCOS7. Since then the syndrome has emerged to be even more heterogeneous, leading to the formulation of different diagnostic criteria to describe the syndrome at best with various degrees of emphasis on the three key diagnostic features8,9.

*National Institute of Health (NIH), 1990 Criteria:* The first description of this syndrome arose from the proceedings of an expert conference sponsored by NIH in April 1990, which summarized the following major criteria: 1) hyperandrogenism and/or hyperandrogenemia, 2) oligoovulation and 3) exclusion of related disorders like androgen secreting tumors, congenital adrenal hyperplasia etc.10. Ultrasonographic evidence of PCO was concluded to be suggestive of PCOS but not necessarily diagnostic20,22. In essence NIH criteria identified PCOS as a disorder of ovarian androgen excess10. The NIH criteria represented a very important step towards establishing a universally accepted clinical definition for PCOS8.

*Rotterdam Criteria, 2003:* In the years that followed, it became apparent that the clinical presentation of PCOS was much more variable than that was described by the NIH criteria, and the polycystic morphology of the ovaries was a consistent finding in women demonstrating biochemical and clinical evidence of the syndrome. Considering these varied presentations, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) formulated another diagnostic criteria in a conference at Rotterdam in May 200311. According to this PCOS was defined by two of the following three criteria in addition to the exclusion of related disorders: 1) hyperandrogenism and/or hyperandrogenemia, 2) oligoovulation and 3) evidence of PCO on ultrasound (presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and / or increased ovarian volume of >10 ml). Unlike previous definitions this requires no subjective assessment of stromal echogenicity and / or follicle distribution pattern. Therefore Rotterdam criteria expanded the NIH criteria and added two additional phenotypes as PCOS, women with 1) PCO and clinical and/or biochemical evidence of androgen excess, but without ovulatory dysfunction, and 2) PCO and ovulatory dysfunction, but without hyperandrogenemia and/or hirsutism (*i.e.* no signs of androgen excess)11. The Rotterdam criteria is currently the most widely accepted criteria12,13. Because of its diverse clinical presentations, considerable debate remains regarding what collection of symptoms constitutes a diagnosis of PCOS and the diagnosisremains one of exclusion13.

**Prevalence:** PCOS is notably the most common endocrinopathy in reproductive years typically presenting in adolescence, though it can occur in later years also (1). The prevalence of PCOS worldwide, using the NIH criteria, in women of reproductive age is between 6.5 and 8%14. Adoption of the 2003 Rotterdam criteria for the diagnosis of this disorder will presumably increase the prevalence of PCOS because the inclusion criteria is broader (1.5 fold higher) compared to the NIH criteria14. In general the prevalence is around 4% to 12% (2). The prevalence also shows ethnic variation14. Population from the Indian subcontinent has a comparatively higher prevalence of PCOS15.

**Pathophysiology of PCOS:** Women with this hyperandrogenic syndrome clinically present with three major symptoms: menstrual irregularity, symptoms and signs of androgen excess and infertility16. The menstrual irregularity is chronic, typically beginning at menarche in the form of menometrorrhagia or oligomenorrhea or amenorrhea. The androgen excess is usually manifested by varying degrees of hirsutism and acne. Also they present with PCO on ultrasound16. It has been observed that these patients have a defect in cyclical follicular maturation and ovulation17.

Normally the combined actions of luteinizing hormone (LH) on theca interstitial cells and follicular stimulating hormone (FSH) on ovarian granulosa cells is necessary for normal ovarian function18. During follicular phase of menstrual cycle, there is an increase in FSH secretion from the anterior pituitary. Follicular growth and steroidogenesis depend on this initial increase in FSH19. Ongoing follicular maturation requires the successful conversion from an androgenic to an estrogenic microenvironment. Theca cells produce androgens in response to LH stimulation which are converted into estradiol by granulosa cells by the aromatase under the influence of FSH20. As the follicle enlarges there is an increased sensitivity to FSH. The granulosa cell’s responses to elevated FSH i.e. an increase in aromatase enzyme, increased estradiol synthesis from androgens and the expression of LH receptors on theca cells are the hallmarks of a successful follicular maturation19. Around mid follicular phase, elevated estrogens exert a negative feedback on pituitary FSH secretion and the FSH levels begin to wane off21. Towards the end of follicular phase, estradiol level increases dramatically which gives a positive feedback at hypothalamus and pituitary to generate a LH surge essential for ovulation and luteinization. The LH surge also promotes androgen synthesis from theca cells which acts as substrate for estradiol synthesis when influenced by FSH. Following ovulation during the luteal phase, corpus luteum forms and steroidogenesis especially of progesterone occur from corpus luteum. Some amount of estradiol also gets secreted. Later disintegration of the corpus luteum causes the steroid levels to fall and provides a feedback for FSH increase, thereby initiating the next cycle19. Figure 1 shows the hormonal changes during a ovulatory cycle21.

In this whole process of follicular maturation, the concentration of androgens plays a critical role. In low physiological levels, androgens enhance aromatase activity and facilitate estrogen production. At higher concentration, the granulosa cells favour conversion of testosterone to more potent 5α reduced androgens i.e. dihydrotestosterone that cannot be converted into estradiol in ovary. The raised ovarian androgen levels also lead to follicular atresia19. The higher amount of androgens enters into circulation & more extraovarian aromatization occurs in skin and adipose tissue5.

It has been evidenced that in PCOS, ovarian hyperandrogenism accounts for most of the symptoms18. The underlying pathophysiologic defect leading to hyperandrogemia and anovulation remains unknown and has been a source of controversy. However, two key features including abnormal gonadotropin dynamics & IR have been found to have constant association with PCOS22.

*Gonadotropins:* Women with PCOS have higher mean concentration of LH and relatively low levels of FSH in comparison to normal women. The increase in LH pulse frequency and particularly the amplitude is due to heightened sensitivity of pituitary to gonadotropin releasing hormone (GnRH). Also an enhanced pulsatile secretion of GnRH has been observed5. Since these patients are anovulatory, they lack cyclical synthesis of progesterone and so the negative feedback on LH secretion is lost18. Increased LH is associated with accelerated daily production of androgens especially androstenedione & testosterone in theca cells. The increased androgens enter into circulation and undergo extraovarian aromatization to estrone in skin and adipose tissue23,24. Therefore, PCOS is not only a state of hyperandrogenism but also a hyperestrogenic state. Elevated estrogens exert an abnormal feedback at the level of hypothalamus and pituitary and correlate with increased LH and diminished FSH levels23. The decreased FSH and elevated androgens impair follicular maturation & produce atresia which in turn lead to anovulation5.

*Insulin Resistance:* Recently hyperinsulinemia and IR has been postulated in the pathogenesis of PCOS25. IR is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in the normal population5. It occurs either due to hereditary defects or acquired later in life. IR has been evidenced in both obese and non-obese patients. The underlying mechanism has been found to be post receptor-binding defects in insulin signaling pathways6,25. Insulin acts via its own receptors on ovary and produces enhanced thecal stimulation, resulting in increased level of androgen and estrogen. Apart from the action on ovary, insulin also has some role in decreasing hepatic synthesis of sex hormone binding globulin (SHBG) and insulin like growth factor binding protein-1 (IGFBP-1)5,6. SHBG binds to testosterone and estradiol and decreases their biological activity. A fall in the level of SHBG will increase the circulating testosterone and estrogen levels. Similarly IGFBP-1 binds to insulin like growth factor-1 (IGF-1) and so decreased levels of IGFBP-1 will enhance the effects of IGF-1. IGF-1 acts via its own receptor on ovary and has actions similar to that of insulin6,25. Studies have shown that hyperandrogenism itself can produce IR26. Ovarian hyperandrogenism and IR have become the vicious cycle of PCOS & one can aggravate the other25. Therefore the pathophysiology of PCOS is complex involving the hypothalamic – pituitary ovarian axis, ovarian thecal cell hyperplasia and IR27.

**Co-Morbidities In PCOS:** Obesity is a very common clinical feature in women with PCOS. Around 50% of patients are either overweight or obese. History of weight gain frequently precedes the occurrence of oligomenorrhea and hyperandrogenism suggesting a pathogenetic role. Most of them have android type of obesity28. Increased amount of adipose tissue has a detrimental effect on whole body sensitivity to action of insulin and glucose tolerance29. IR reduces the tyrosine kinase activity of the insulin receptor, thereby decreasing the signal transduction pathway. Alternatively post receptor binding defects have also been proposed28. But studies have revealed the occurrence of IR in subjects with both obese and normal BMI30. Therefore obesity accentuates and maintains the underlying IR in patients with higher BMI28. Also the elevated androgens act in synergy with IR and they also exacerbate each other31. This is further supported by studies which have revealed improvement in ovulatory rates and decrease in IR and androgen levels after metformin therapy32. These three prime factors namely *hyperandrogenism, hyperinsulinemia and obesity* act in concert leading to further metabolic abnormalities. The most common metabolic abnormality encountered is dyslipidemia. Around 70% of these patients exhibit an atherogenic lipid profile27. Also recently an alteration in thyroid status, in the form of hypothyroidism in the subjects with PCOS has been observed. Hypothyroidism can in fact worsen the symptoms of PCOS by decreasing the SHBG levels and increasing the androgen levels33. The interaction among all these long term risks places PCOS as an independent determinant for the development of type 2 diabetes mellitus, hypertension and cardiovascular diseases27.

**Cardiovascular Risks In PCOS :** PCOS is a syndrome where all the cardiovascular risks have been meticulously interlinked. Studies have revealed both structural and functional abnormalities of the cardiovascular system in PCOS. Microvascular changes in the form of atherosclerosis and arterial calcification have been reported in these patients31. Endothelial dysfunction has been postulated to be the underlying pathogenetic mechanism for the development of the vascular alterations. Endothelial dysfunction presents not only in the form of impaired vasodilation but also as increased vascular stiffness31. The ability of the endothelial cells to synthesize various chemical mediators in a regulated and balanced manner maintains the vascular homeostasis and tone34. The most notable mediators involved in maintenance of vascular health is the nitric oxide (NO) and endothelin34. The synthesis of NO occurs via the PI3Kdependent signaling pathways and the MAPK-dependent pathways leads to the synthesis of endothelins. Impaired synthesis of nitric oxide and increased production of endothelin-1has been causally connected to the genesis of endothelial dysfunction31. Insulin resistance, has been postulated to have significant implication on the development of vascular dyshomeostasis34. High levels of insulin selectively impair the signaling via PI3K pathways and reduce production of endothelial NO whereas MAPK-dependent pathways are unaffected. Thus the unaltered MAPK-dependent pathways are overactive, which not only increases the vascular tone but also causes increased proliferation of the vascular smooth muscle34.

There also occurs increased production of reactive oxygen species due to hyperinsulinemia in the endothelial cells which concomitantly leads to the prothrombotic state34. Certain other abnormalities in the form of early left ventricular diastolic dysfunction and low ejection fraction have also been evidenced, which could be attributed to the dyslipidemia and hypertension31.

Hyperandrogenism is also known to cause hypertension in women with PCOS, though underlying pathogenetic mechanism is not fully understood35. Elevated testosterone have also been to postulated to accelerate the plaque formation36. Apart from that, hypothyroidism can independently affect the cardiovascular system37. Hypothyroidism increases the risk for development of hypercholesterolemia, diastolic hypertension and prolonged QT interval37. PCOS is also a state of inflammation. Elevated levels of C-reactive protein (CRP) have been noted in PCOS38. CRP is an independent contributor of cardiovascular pathology. It binds selectively to oxidized LDL in atheromatous plaque and contributes to the pathogenesis, progression of the atheroma39.

With the increasing prevalence of PCOS and its significant implications on cardiovascular disease, it warrants an early assessment of cardiovascular status and health31. In the last few decades a significant relation between the adverse cardiovascular events and autonomic dysfunction has been evidenced40. PCOS which originates from an altered hormonal milieu has significant coexistent risk factors including IR, dyslipidemia and obesity which can independently tax the ANS and affect the cardiovascular autonomic modulation in these patients. The assessment of cardiovascular autonomic modulation in the form of sympathovagal balance would provide an early insight into the derangement in CV health.

**IMPORTANCE OF SYMPATHOVAGAL BALANCE AND IMBALANCE**

**The Concept of Sympathovagal Balance:** Emotional responses of the body and responses to environment occur without conscious knowledge of the individual. These responses are therefore, called autonomic responses that are executed through the autonomic part of the nervous system, known as autonomic nervous system (ANS)41. Through its innervation to all visceral organs of the body ANS controls all major functions of the body such as circulation, respiration, digestion, excretion, reproduction, immunity, metabolism etc. ANS executes its functions through its two major subdivisions: the sympathetic and the parasympathetic. Broadly, sympathetic system is the system of energy mobilization and utilization, and parasympathetic is the system of energy restoration and storage41. Though these divisions of ANS are physiologically opposite, they are reciprocal to each other in their outflow and functions. Normally, body tries to maintain a balance between the storage and utilization of energy by balancing the parasympathetic and sympathetic activities. In a healthy individual, sympathetic and parasympathetic (vagal) systems are in dynamic balance, which is known as sympathovagal balance that contributes to attain an effective internal homeostasis42.

**Sympathetic and Parasympathetic Activity and Reactivity:** The sympathetic neurons display activity at rest, and therefore, impart basal influence on functions of the organs they innervate. The rate of sympathetic discharge in resting condition is called basal sympathetic drive or sympathetic tone41. Assessment of basal sympathetic drive to heart by spectral analysis of heart rate variability (HRV) reflects the sympathetic tone of the individual and is considered as an important sympathetic functions test43. Rate of discharge in sympathetic neurons increases following application of various stimuli, for example the autonomic response to orthostatic stress. This is called sympathetic reactivity. Determination of sympathetic reactivity by assessing the change in heart rate and blood pressure response to standing is also a sympathetic function test44. Favorable conditions in both external and internal environments herald the parasympathetic activation. Activity in parasympathetic neurons at rest is called parasympathetic tone or vagal tone. Assessment of basal cardiac vagal drive by HRV analysis is an important parasympathetic function test43. A stronger vagal tone is an index of good health45. However, activities and reactivities of both sympathetic and parasympathetic systems are altered due to the changes in environments. As the systems operate promptly to meet the environmental demands, rapid alterations occur in the reactivities of sympathetic and parasympathetic systems. A dynamic, stable and reciprocal relationship between sympathetic and parasympathetic systems is the cornerstone of sympathovagal balance. Failure to react or excess reactions and persistent reaction of one component or both the components of ANS to environmental stresses leads to sympathovagal imbalance43.

**Sympathovagal Imbalance and its Related Dysfunctions:** Sympathovagal imbalance is a state of functional disharmony in which one component of the ANS dominates over the other. In sympathovagal imbalance, usually the sympathetic system is hyperactive and the parasympathetic system is hypoactive42. Hyperactivation of sympathetic system for a longer period of time leads to excessive drainage of energy from the body and failure to meet or replace this loss or demand ultimately results in degeneration. Usually with persistent sympathetic activation, parasympathetic system is suppressed. In fact, in chronic sympathovagal imbalance, occurrence of vagal inhibition aids to the deleterious impact of the sympathetic activation. Nevertheless, the vagal withdrawal could also be the primary initiating factor of sympathovagal imbalance42. There is growing evidence that the dysfunction of ANS in the form of sympathovagal imbalance is involved in the etiopathogenesis of premature aging and wide range of diseases40. It is worth declaring that sympathovagal imbalance is the major mechanism of many morbidities and comorbidities, and could possibly be the final common pathway of degeneration and death40.

Spectral analysis of heart rate variability (HRV) is a sensitive measure of sympathovagal balance or imbalance46,47. HRV analysis is widely used to evaluate the nature and magnitude of autonomic imbalance in various clinical disorders including cardiovascular dysfunctions, and to assess the morbidities and mortality46-48. The frequency domain indices of HRV such as total power (TP), high frequency power (HF), normalized high frequency power (HFnu), and time domain indices of HRV such as mean heart rate (mean RR), square root of the mean squared differences of successive normal to normal intervals (RMSSD), standard deviation of normal to normal interval (SDNN), the number of interval differences of successiveNN intervals greater than 50 ms (NN50), the proportion derivedby dividing NN50 by the total number of NN intervals (pNN50) and the HRV triangular index are measures of parasympathetic activity or vagal drive47,49. The low frequency power (LF), and normalized low frequency power (LFnu) are measures of sympathetic activity and the ratio of low frequency power to high frequency power (LF-HF ratio) is the measure of sympathovagal balance47.49. The magnitude of heart rate variability, i.e., the quantum of the total power (TP) of HRV is an independent predictor of mortality50,51. Decreased HRV is a risk factor for cardiovascular disease morbidity and mortality52-55. In most of the studies, LF-HF ratio, the sensitive marker of sympathovagal imbalance was high indicating a greater sympathetic dominance in high risk groups50-55. Especially, in the Hoorn Study, which as a prospective study of nine-year follow-up period, the HRV indices were significantly correlated with high risks in patients suffering from diabetes, hypertension and cardiovascular diseases after controlling for age, gender and glucose tolerance51.

**Sympathetic Overactivity and Vagal Withdrawal:** Many studies on HRV analysis for risk stratification have reported the predominant role of sympathetic overactivity in the genesis of cardiovascular diseases51. However, the role of decreased vagal activity (vagal withdrawal) in the causation of cardiovascular dysfunctions has not been adequately analyzed and remains under-reported. Nevertheless, in the Atherosclerosis Risk in Communities (ARIC) study and Autonomic Tone and Reflexes After Myocardial Infarction (ATRIMI) study, the decrease in HF power, the putative marker of vagal withdrawal was correlated with incident myocardial infarction and incident coronary heart disease53,54. In these studies, the decreased HRV and decreased HF power were found to be associated with increased morbidity and mortality. Similarly, the report of Camm AJ et al on post-myocardial infarction with depressed left ventricular function, the HRV triangular index and low HRV were observed to be the significant independent predictor of mortality after controlling for age, gender, LV ejection fraction, diabetes, and beta-blocker use55. Thus, few studies have revealed the contribution of vagal withdrawal in the genesis of sympathovagal imbalance and in the prediction of morbidity and mortality in high risk populations.

**Sympathovagal Imbalance In PCOS:** The magnitude of alteration in the hormonal milieu and the metabolic profile in PCOS makes them the potential candidates for the development of cardiovascular autonomic dysfunction. The sympathovagal imbalance in PCOS has been evidenced through various studies. Studies have revealed a decrease in heart rate recovery (HRR) following exercise in these patients. Attenuation of HRR suggests a depressed vagal modulation56. Also, the recovery of SBP following exercise was delayed in them, which reflects a sympathetic overactivity56. The studies carried out to assess the HRV have also revealed an altered autonomic status. There was an increased LFnu reflecting an exaggerated sympathetic drive and decreased HFnu, depicting an attenuated vagal modulation. The LF-HF ratio which is the marker of sympathovagal balance was elevated among patients with PCOS, which depicts the prevailing sympathetic overactivity and decreased HRV in them57. There are studies which have reported the decreased HRV as a significant cardiovascular risk factor49. Also an increased sympathetic and decreased parasympathetic modulation is a marker of poor cardiovascular health as evidenced from studies on patients with myocardial infarction49. PCOS has a constellation of factors which can cause this autonomic dysfunction. Obesity has long been known to cause derangement in autonomic functions in the form of increased adrenergic drive and lowered vagal modulation58,59. In addition the presence of android obesity accentuates the derangement60. IR which has been postulated as one of the pathogenetic mechanism, is also known to cause sympathetic overactivity61. Studies have postulated that an increased sympathetic activity and decreased parasympathetic activity also promotes IR thereby causing a vicious cycle62. Dyslipidemia, the most common metabolic derangement in PCOS, has also been interlinked to autonomic imbalance each factor promoting the development of the other63,64. Alteration in thyroid hormone levels is known to have significant implication on ANS. The elevated thyroid hormone levels are known to increase the adrenergic drive65.

**Conclusion:** PCOS is a heterogeneous syndrome with a significant alteration in autonomic modulation in the form of increased adrenergic drive and a depressed vagal activity. The various co-morbidities associated with PCOS namely, increased adiposity in specific the abdominal obesity, insulin resistance, dyslipidemia, hyperandrogenism and altered thyroid profile all have a significant implication in the underlying autonomic dysfunction. And the autonomic imbalance itself can further accentuate the already existing co-morbidities. The accentuated adrenergic drive makes these patients highly prone for the development of hypertension and cardiovascular diseases. IR and increased adiposity heightens the risk for an early development of type 2 diabetes in them, in addition to their additive role along with dyslipidemia in potentiating atherogenesis.

Therefore, an early diagnosis and intervention becomes mandatory in restoring the normal cardiovascular functions. Assessment of autonomic functions has proved to be a sensitive tool in diagnosing the early features of CV dysfunction in the form of autonomic imbalance. When detected early, it enables an early intervention to yield a better cardiovascular health to these patients. The simplest approach of restoring the sympathovagal balance would be to advise the life style modifications in the form of regular exercise. Regular exercise decreases the adiposity and improves the sensitivity of insulin in the peripheral tissues66,67. Studies have also reported increased parasympathetic modulation with weight loss68. So this would break the vicious cycle of the interlinked risk factors. Also the increased insulin sensitivity would complement and supplement the medical therapy advocated to these patients and would lead to better outcome in both reproductive and cardiovascular health.

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