Applying a Women's Health Lens to Endocrine and Metabolic Disorders

Women's health is already a global priority and poised to emerge as an even greater and more urgent one for the post pandemic world. Women's roles in their homes, their workplaces, the community and on the world stage have evolved and so have their health needs and challenges. The traditional practice however has been one of viewing women's health through the narrow lens of sexual and reproductive health. The focus of this editorial is to deepen the understanding to include gender as a determinant of health and shine the light on all aspects of women's health with a special focus on endocrine and metabolic disorders.

The theme for International Women's Day 2021 is "Choose to Challenge." A challenged world is an alert and aware world and one that is certain to promote equity and improve outcomes. We as endocrinologists and diabetologists can challenge the many implicit biases, stereotypes, and gender norms that have colored the practice of medicine and partner in evangelizing the concept of a gender transformative approach in clinical practice.

Women's health is the net result of the interplay between their hormones, gender, sex, genetics, biology, and their socio-cultural environment. The field of endocrinology and metabolism is undeniably the most influenced by this cluster of variables than any other discipline in all of Medicine. Hormones play a critical role in defining the biological basis of sex differences and a very pivotal role in a woman's health throughout her life.[1] The human endocrine system is complex, yet fascinating in its remarkably predictable feedback loops and cyclical reproductive function and clockwork precision with menarche, ovulation, and the menopause. Endocrine disorders like hypothyroidism and obesity have a disproportionately higher prevalence in women, conditions like polycystic ovary syndrome, and gestational diabetes are unique to women, while major global public health threats like osteoporosis and diabetes have starkly different risk factors, drivers, and clinical outcomes in women.

The narrative has largely been centered on genes and hormones that determine sex and biology, while there is an acute need to highlight the role played by gender, especially in the realm of women's health. Our objectives will be addressed if we recognize, appreciate, and apply gender differences while exploring pathophysiology, therapeutic interventions, and preventive strategies. Some of the more frequent clinical challenges encountered in the practice of Endocrinology tell the tale more clearly.

Diabetes Mellitus

Overwhelming evidence has accrued over the past decade on how diabetes is different, more difficult, more distressing, and deadlier in women. The lifetime risk of diabetes is higher in women.[2] The prevalence of prediabetes in young women of India is alarming with conversion to overt diabetes as they age.[3] Women of reproductive age with preexisting type 1 or type 2 diabetes are at unacceptably high risk for pregnancy-related complications, pregnancy losses, preterm births or delivering babies with serious birth defects.[4]

Women are particularly vulnerable to the myriad complications of diabetes and this heightened susceptibility remains a puzzle. Cardiovascular disease, depression, stroke, fractures, and cancer are all disproportionately higher in women. A large meta-analysis (858,507 individuals, n = 28,203 events) has shown that women have a 44% greater risk for incident cardiovascular disease than men with diabetes.[5] Women with diabetes are at much greater risk for cancer [26% greater than women without diabetes], a fact seriously neglected by most.

Women with diabetes are also challenged by poorer glycemic control[6] and greater prevalence of cardiovascular risk factors like high BMI, atherogenic lipid profile, depression, and other mental health issues. This is further compounded by their own poor health-seeking behavior and health care systems that have been notoriously gender unequal. All this has translated into much higher mortality in women across the globe.[7]

What could be responsible for these unfortunate but very real differences? Does the clock start to tick earlier in women? Are there nontraditional risk factors that play an outsized role? Are estrogens the culprit? Are the social determinants of health at play? Is it the Yentl syndrome?[8] The truth probably is that all these factors are at play along with something else yet to be identified and studied.

Hypothyroidism

Thyroid disorders, especially hypothyroidism, seems almost exclusive to women largely due to their propensity to develop autoimmune disorders. Women are also frequently burdened with a diagnosis of subclinical hypothyroidism due to the higher prevalence of obesity, predisposition to auto immune disorders, and lower cut offs of TSH used in infertility management, preconception care, and pregnancy. The Wickham survey (initial and follow-up)[9,10] showed a significantly higher prevalence of hypothyroidism and goiters in women.

Women may present with certain unique symptoms like menorrhagia secondary to anovulation or an acquired Von Willebrand syndrome or galactorrhea and hyperprolactinemia secondary to the TSH and TRH elevation.[11] Young girls may present with precocious puberty due to the Vanwyk–Grumbach syndrome.[12] Evaluation strategies, diagnostic thresholds, and management do not differ for women. However, the disproportionately high prevalence of obesity and thyroid auto immunity in women presents clinicians with challenges when addressing subclinical hypothyroidism.

Thyroid physiology undergoes dramatic changes during pregnancy. TSH receptor is stimulated by human chorionic gonadotropin; estrogens stimulate the production of thyroxine binding globulin leading to marked elevations in total hormones and a suppression of TSH in the first trimester of pregnancy. Untreated subclinical and overt hypothyroidism has been associated with pregnancy losses, hypertensive disorders in pregnancy, and even gestational diabetes.[13] Optimizing TSH to recommended trimester specific range with thyroxine is the standard of care. Newborn screening for congenital hypothyroidism is required by the law in many countries and should be actively promoted by endocrinologists in their institutions.

Hyperthyroidism, goiters, nodules, and thyroid cancer are also more frequently observed in women. The female to male ratio for papillary thyroid cancer is typically 2.5: 1.0. Postpartum thyroiditis occurs in 5%–12% of women post-delivery and needs a high index of suspicion for early recognition and treatment. 30%–40% of women develop overt hypothyroidism in the following years[14] making annual follow-up a proactive and smart strategy.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is believed to be the most common endocrine disorder of women of reproductive age. In India, over 300 million women are between the ages of 15–49 years and even a conservative estimate of 10% raises the potential number of women with PCOS to staggering highs. Multiple guidelines, changing clinical presentations across the woman's life span, lack of a single therapeutic strategy, stigmatization, and misinformation have made PCOS an even greater enigma.

Recommendations for a name change to metabolic reproductive syndrome have been made[15] and this offers a potential opportunity to revitalize the campaign to educate and empower health care providers and patients on the metabolic risks (diabetes and gestational diabetes)[16] and redirect our attention to cardiovascular health, mental health, and cancer screening and prevention.

As hormone specialists, the onus is also on us to rule out Cushing's syndrome, premature ovarian failure, congenital adrenal hyperplasia, prolactin excess, androgen producing tumors of the ovary and adrenal[17] while evaluating a woman referred for evaluation of hirsutism, amenorrhea, anovulation, obesity, infertility, or glucose intolerance. Adolescent PCOS is an even greater challenge requiring a watchful approach and a greater focus on metabolic issues, lipid abnormalities, and androgen excess.

PCOS requires us to empower ourselves with the knowledge and tools to recognize and manage psychosocial challenges stemming from eating disorders, body image issues, infertility-related difficulties, and low self-esteem due to stigmatization.

PCOS is the classic example in women's health where there needs to be cross talk between specialties like Endocrinology, Obstetrics and Gynecology, Cardiology, Mental health, Oncology, and Dermatology.

Obesity

An endocrinologist's role in weight management is not merely that of a detective, ruling out thyroid dysfunction, Cushing's syndrome, hypothalamic disorders, Prader–Willi syndrome, or other dysmorphic forms of obesity but to take a deeper dive into metabolism, lifestyle, body composition, metabolic risks, and gain insight into the origin of the weight gain. This is particularly relevant for women who battle eating disorders, peer pressure, body image issues, and difficulty with conception.

Appetite regulation and energy metabolism are intriguing and remain a puzzle. Estrogens, ghrelin, leptin, and a host of other hormones regulate satiety and hunger and metabolism.[18] Estrogen receptors are present in adipose tissue and female sex hormones play a major role in the amount, distribution, and metabolism of fat in women. Menstrual cycles, pregnancy, and the menopause are times of estrogen fluctuations with corresponding changes in appetite and or body fat.

Obesity in girls and women carries a very high risk for the development of type 2 diabetes, gestational diabetes, certain cancers and cardiovascular diseases, osteoarthritis, and low self-esteem due to body shaming and societal norms and expectations.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is possibly the most debated, evolving, and urgent metabolic challenge facing us. A staggering number of women (20 million) are affected worldwide, with 25% or more of the pregnancies in South Asia complicated by hyperglycemia in pregnancy.[19] Every aspect of GDM is up for debate, from definition to monitoring to management. The rise in detection of overt diabetes and hyperglycemia at first booking is a disturbing trend. The pressing issue now facing the endocrine and Ob Gyn community is to address hyperglycemia in early pregnancy or prevalent GDM.[3]

While several questions remain unanswered, a proactive approach before, during, and after pregnancy presents us

with a great opportunity to decrease the burden of diabetes and other noncommunicable diseases (NCDs) in women and their offspring.

Prevention of GDM through preconception care and inter pregnancy care and post-partum follow-up of women with GDM are in the domain of the endocrinologist/diabetologist and this could be our best strategy for decreasing the burden of diabetes and other NCDs in women and the next generations. Pregnancy should be viewed as the window to future chronic disease.[20]

The metanalysis by Gadve and colleagues published in this issue of the journal highlights the enormous public health challenge posed by GDM. Selection of just 6 studies from 1276 initial studies reveals the rigor and care in choosing studies that fit the inclusion criteria. The cumulative incidence of T2DM was 17.34% and when follow-up done for more than 10 years the cumulative incidence of T2DM was 33.00%. The risk of developing diabetes was 10.81 times higher in women with GDM compared to women without. This analysis and the current low level of awareness make a strong case to launch a movement to develop communication strategies and tools for education of women of reproductive age and their health care providers. Endocrinologists could help play a big role in doing the heavy lifting.

Menopause

Menopause is the culmination of a long reproductive phase in every woman's life. The age at menopause has stayed relatively constant around 47–50 years while life expectancy has increased significantly in the last few decades. However, dramatic changes in sex hormones, body composition, lipid profile, and bone mass make this a window of opportunity to initiate screening and prevention programs for healthier aging. While the hormonal changes at the menopause are natural and expected, many women are distressed by vasomotor symptoms, mood changes, and memory issues (mental fog).

Observational studies and the popular belief that menopause is a state of hormone deficiency had encouraged the prescription of hormone therapy as a panacea for menopausal ailments and as a youth pill. The Women's Health Initiative published nearly two decades ago[21] changed this perception and practice patterns on its head. Use of hormone therapy is now limited to women with premature or early menopause up to the natural age for menopause. Women with vasomotor and genitourinary symptoms do benefit from hormone therapy but it needs to be tailored, monitored, and done with the women involved in a shared decision-making process. Lower doses, shorter duration, alternate routes, and an evidence-based approach are a key to acceptance and safety.

Osteoporosis and Bone Health

The many folds higher risk for osteoporosis and fractures in women has traditionally been attributed to lower peak bone mass, less muscle mass, rapid bone loss at the menopause, and by the impact of pregnancies and lactation on bone health. The salutary role of estrogens on bone health of women is undeniable. Estrogens affect bone mass through multiple mechanisms involving Calcium, PTH, Calcitonin and their effect on Osteoblasts and Osteoclasts and much more.

In addition, risk factors like diabetes (increased risk of fractures in women),[22] cancer, thin stature, premature menopause, and obesity also make women more vulnerable to low bone strength and fractures. The wide array of antiresorptive and anabolic agents now available to treat osteoporosis includes Bisphosphonates, Denosumab, Romososumab, Teriparatide, Abaloparatide, and Raloxifene. Despite the Women's Health Initiative showing a significant benefit in hip fracture reduction, hormone therapy is not recommended for prevention or treatment of osteoporosis. Risk of breast cancer with continued use and quick loss of bone after stopping HT are challenges that have precluded the use of estrogens for bone health. The safer and more potent options listed above have provided the much-needed alternatives.

Use of sunscreens, avoidance of the sun, lack of food fortification, food fads, pregnancy, and lactation make women more prone to Vit D deficiency and contribute significantly to the osteomalacic component of osteoporosis.

Growth and Puberty

Puberty too early or too late has dire consequences for a girl child. Too early (most often idiopathic) could lead to compromised final height, psychosocial issues, vulnerable to sexual abuse, and pregnancies. Puberty too late could be the cause for peer pressure, parental anxiety, and unwarranted and premature use of estrogens leading to abnormal breast development, and delay in diagnosing the cause of pubertal delay.

The paradigm shift in the management of Turner syndrome with growth hormone and a gentle and steady approach to puberty induction is a classic example of advances in female endocrinology.

Solutions for a More Gender Transformative Endocrinology and Metabolism Practice

Awareness

The practice of medicine has largely been either gender blind or gender neutral with a "One Size Fits all" approach. Raising awareness among health workers and the community needs resources, intention, and sustained efforts.

Community-level education requires dedicated, women-centric campaigns like the Go Red program (American Heart Association's program for women). Conditions like PCOS, GDM, and Type 1 diabetes in young women require patient champions and activists and possibly the use of social media and digital health coaching.

Inclusion

Gender differences are a paradox. Women's health needs reimagination of the current approach of addressing it from a reproductive health only paradigm to one that includes a look at all aspects of women's health, especially her fears, challenges, wishes, her environment, and her world. Women's experiences of an endocrine or metabolic condition are often entirely different and including these into our clinical evaluation process is needed for developing targeted solutions.

Research

"Because we have studied women less, we know less about them. The result is that women may not always have received the most optimal care" Dr Janine Clayton Director of the office of research on women's health National Institutes of health.

Inclusion of women in clinical trials and women of reproductive age in endocrinology research will lead to better understanding, better definition, specific solutions, and better outcomes.[23] COVID-19 has shown us how critically important sex disaggregated data reporting is.

Guidelines

Gender and sex specific guidelines do not merely provide a roadmap but can serve as a reminder to address the patient using the gender lens, steer clinicians toward proven therapies in women, and promote scientific rigor in clinical decision making. Sex differences have traditionally not always been incorporated into clinical decision making. It is time for gender specific guidelines for many of the endocrine and metabolic disorders. Diabetes is the perfect example. Over 200 million women with diabetes need tailored treatment protocols factoring in contraception, preconception care, postpartum follow-up, safety of medications during pregnancy and lactation, impact on weight, bone health, cardiovascular risk, and mental health. Also, women's financial status may promote use of generics, cheaper alternatives, and missing of doses by rationing them. These realities must be in our radar while considering treatment options for diabetes and other endocrine and metabolic disorders.

Education

Education involves building a culture of gender mainstreaming in the institution and teaching the art of caring for girls and women as an integral part of personalized medicine. Health care providers can dramatically alter the outcomes simply by "listening" to women. Their experiences are different and relevant and their narrative unique.

Women are change makers and gate keepers of their family's health and educating a woman will also have a ripple effect on the message reaching millions more.

Leadership

Elevating women into positions of leadership in academia, medical institutions, boards of medical societies, and in decision making roles has been consistently shown to lead to better outcomes. Consciously promoting equal representation in committees, scientific programs, academic appointments, grant allocation, and publications is a great start.[24] This helps promote the women's health agenda as well.

Way Forward

COVID-19 has halted or rolled back the progress made in many areas of women's health due to funding limitations, redirection of human resources, and de prioritization of programs. This pandemic has also shown us that several of the endocrine and metabolic disorders that we manage are major risk factors for COVID-19. We are in a unique position to study this relationship and leverage this once in a lifetime opportunity to raise awareness regarding diabetes, obesity, polycystic ovary syndrome, gestational diabetes, steroid use, physical activity, and good nutrition to name a few.

Endocrinologists and diabetologists hold the key to lowering the burden of major chronic diseases by focusing on women, their life cycle, and their unique challenges and needs.

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References

1. Lauretta R, Sansone M, Sansone A, Romanelli F, Appetecchia M. Gender in endocrine diseases: Role of sex gonadal hormones. Int J Endocrinol 2018;2018:4847376.
2. Luhar S, Kondal D, Jones R, Anjana RM, Patel SA, Kinra S, *et al*. Lifetime risk of diabetes in metropolitan cities in India. Diabetologia 2021;64:521-9.
3. Simmons D. Paradigm shifts in the management of diabetes in pregnancy: The importance of type 2 diabetes and early hyperglycemia in pregnancy: The 2020 Norbert Freinkel award lecture. Diabetes Care 2021;44:1075-81.
4. Deepa M, Grace M, Binukumar B, Pradeepa R, Roopa S, Khan HM, *et al*. High burden of prediabetes and diabetes in three large cities in South Asia: The center for cArdio-metabolic risk reduction in South Asia (CARRS) study. Diabetes Res Clin Pract 2015;110:172-82.
5. Sina M, MacMillan F, Dune T, Balasuriya N, Khouri N, Nguyen N, Jongvisal V, Lay XH, Simmons D. Development of an integrated, district-wide approach to pre-pregnancy management for women with pre-existing diabetes in a multi-ethnic population. BMC pregnancy and childbirth 2018 Dec;18:1-4.
6. IDF Diabetes Atlas Group. Diabetes Research and Clinical Practice 2015;109:461-5.
7. Rossi MC, Cristofaro MR, Gentile S, Lucisano G, Manicardi V, Mulas MF, *et al*. Sex disparities in the quality of diabetes care: Biological and cultural factors may play a different role for different outcomes: A cross-sectional observational study from the AMD annals initiative. Diabetes Care 2013;36:3162-8.
8. Guastamacchia E, Triggiani V, Aglialoro A, Aiello A, Ianni L, Maccario M, *et al*. Italian Association of clinical endocrinologists (AME) & Italian Association of clinical diabetologists (AMD) position statement: Diabetes mellitus and thyroid disorders: Recommendations for clinical practice. Endocrine 2015;49:339-52.
9. Healy B. The Yentl syndrome. N Engl J Med 1991;325:274-6.

10. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, *et al*. The spectrum of thyroid disease in a community: the Whickham survey. Clinical endocrinology. 1977;7:481-93.
11. Michiels JJ, Schroyens W, Berneman Z, van der Planken M. Acquired von Willebrand syndrome type 1 in hypothyroidism: Reversal after treatment with thyroxine. Clin Appl Thromb Hemost 2001;7:113-5.
12. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism. An example of hormonal overlap in pituitary feedback. J Pediatr 1960;57:416-35.
13. Ma L, Qi H, Chai X, Jiang F, Mao S, Liu J, *et al*. The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: A prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. J Matern Fetal Neonatal Med 2016;29:1391-4.
14. Barranco C. Long-term follow-up of women with postpartum thyroiditis. Nat Rev Endocrinol 2006;2:64.
15. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010;8:41.
16. Pan M-L, Chen L-R, Tsao H-M, Chen K-H. Relationship between polycystic ovarian syndrome and subsequent gestational diabetes mellitus: A nationwide population-based study. PLoS One 2015;10:e0140544.
17. Williams T, Mortada R, Porter S. Diagnosis and treatment of polycystic ovary syndrome. Am Fam Physician 2016;94:106-13.
18. Hirschberg AL. Sex hormones, appetite and eating behaviour in women. Maturitas 2012;71:248-56.
19. IDF (prevalence-of-gestational-diabetes-mellitus--gdm----), 2019 (IDF%20(prevalence-of-gestational-diabetes-mellitus--gdm----)%20(2).pdf).
20. Arabin B, Baschat AA. Pregnancy: An underutilized window of opportunity to improve long-term maternal and infant health-an appeal for continuous family care and interdisciplinary communication. Front Pediatr 2017;5:69.
21. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. JAMA 2002;288:321-33.
22. Kaur P, Anjana RM, Tandon N, Singh MK, Mohan V, Mithal A. Increased prevalence of self-reported fractures in Asian Indians with diabetes: Results from the ICMR-INDIAB population based cross-sectional study. Bone 2020;135:115323.
23. Liu KA, Dipietro Mager NA. Women's involvement in clinical trials: Historical perspective and future implications. Pharm Pract (Granada) 2016;14:708.
24. Dunne JL, Maizel JL, Posgai AL, Atkinson MA, DiMeglio LA. The women's leadership gap in diabetes: A call for equity and excellence. Diabetes Care 2021;44:1734-43.

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