Abstract

Juxtaposed with monumental improvement in maternal-fetal outcomes over the last century, there has been the recent emergence of rising rates of gestational complications including preterm birth, operative delivery, and gestational diabetes. At the same time, there has been a burgeoning problem with widespread vitamin D de fciency among populations of many developed nations. This paper provides a brief review of potential health outcomes recently linked to gestational vitamin D de fciency, including preterm birth, cesarean delivery, and gestational diabetes. Although immediate costs for obstetric complications related to gestational vitamin D insu f ciency may be f l'

Keywords: Maternal; Pediatric; Health; Gestational; Vitamin D

Introduction and Background

In the early and mid-1800s, the maternal mortality rate in some European obstetrical clinics approached 1 in 5 women as a result of puerperal fever. With the epic discovery of the origins of this "childbed fever" by Ignaz Philipp Semmelweis in the mid-19th century and the eventual knowledge translation of his simple hand washing technique into the clinical domain, rates of postpartum mortality eventually decreased [1]. Over the subsequent century, there continued to be monumental advances in many areas of Maternal-Fetal Medicine. Along with a profound decline in maternal mortality from 7.2 deaths per 1000 births in the early 1900s to 0.08 by the end of 2000, there was a concomitant decline in infant mortality from 96 to less than 7 deaths per 1000 live births. With ongoing research and study over the last decades, remarkable advances have continued to be made in the assessment and management of a variety of gestational and perinatal challenges. Despite much success, however, there are new and emerging concerns in the early 21st century within the eld of Maternal-Fetal Medicine. Along with an astonishing rise in the rate of cesarean delivery with attendant complications to the human micro biome [2], we have witnessed a concerning escalation in preterm birth, a complication associated with higher rates of long-term physical and mental health problems in the o spring. e Institute of Medicine (IOM) estimated the annual costs for the burden of morbidity, disability, and mortality associated with preterm birth in the United States to be at least $ 26.2 billion. Furthermore, the costs associated with neonatal intensive care, healthcare now required by an increasing percentage of the newborn population, are staggering. It is also evident that maternal complications do not necessarily stop with giving birth. Rates of serious obstetrical complications such as postpartum depression, for example, extract enormous personal cost and remain a serious and widespread problem [3]. In addition, there is increasing discussion in the literature about fetal origins of pediatric and adult disease, resulting from potentially modi able gestational determinants such as disordered maternal nutrition and toxic exposures. As this is a new area of study, however, the extent of sequelae associated with modi able gestational determinants is yet unrecognized; it is thus not possible to assign precise costs associated with long-term outcomes. It is important, however, to explore and implement clinical approaches during the preconception and gestational period which address determinants of suboptimal outcomes in order to maximize the environmental domain, there appear to be only two determinants which make up the environment sphere. (i) Are we getting what we need? (ii) Are we being exposed to things that are toxic? Accordingly, it appears that the bulk of human disease, including problems in pregnancy, is related to de ciency and toxicity evidence in the obstetric literature appears to support this contention and provides opportunity to make advances with regard to maternal and fetal well-being. In fact, medical intervention and maternal education delivered prior to conception (preconception care) to secure nutritional adequacy and preclude toxic exposures are being extolled as the next frontier of maternal and child healthcare. e March of Dimes, a nonpro t organization dedicated to the health of mothers and babies, suggests that "the [physician] must take advantage of every health encounter to provide preconception care and risk reduction before and between

***Corresponding author:** Stephen J Genuis, Faculty of Medicine, University of Calgary and University of Alberta, 2935-66 Street, Edmonton, AB, Canada T6K 4C1, E-mail: sgenuis@ualberta.ca

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conceptions-the time when it really can make a di erence" [5]. With the evident link between fetal determinants and later onset disease, measures to secure an optimal gestational environment can have a profound impact on maternal and pediatric health with enormous personal, social, and nancial savings. ere is considerable attention in the literature to the direct link between assorted toxicants in pregnancy and adverse maternal and fetal outcomes. Most recently, FIGO (e International Federation of Obstetrics and Gynecology) released a special communication highlighting the urgent need to address the issue of widespread toxicant exposure and bioaccumulation in reproductive aged women. In addition, it is becoming increasingly apparent that various nutritional de ciencies are widespread and may have an enormous impact on subsequent maternal and fetal health. Increasing evidence appears to con rm that at no point throughout the life cycle is it more important to secure adequate nutrient intake than in pregnancy. is fact, for example, accounts for the emphasis on folate su ciency in early gestation as well as the increased study into the outcomes related to gestational de ciency of required omega3 fatty acids and magnesium. With the emerging evidence that vitamin D acts epigenetically in the regulation of over 2700 di erent genes, there has been much recent research exploring the widespread prevalence of vitamin D de ciency through the continuum of life, including the gestational and neonatal period. is paper is designed to review the literature ndings about the enduring impact of gestational vitamin D su ciency on maternal and pediatric health and well-being.

Methods

is brief review was prepared by assessing available medical and scienti c literature from Medline as well as by reviewing several books, nutritional journals, conference proceedings, government publications, and nutrition related periodicals. Terms searched included gestational vitamin D, pregnancy and vitamin D, fetus and vitamin D, nutrition in pregnancy, as well as pediatric health and vitamin D. Relevant references found in these publications were also searched in order to glean pertinent information. A primary observation, however, was that limited scienti c literature is available on the issue of gestational vitamin D insu ciency as it relates to long-term health outcomes.

e format of a traditional integrated narrative review was chosen as such reviews play a pivotal role in scienti c research and professional practice in medical issues spanning di erent medical disciplines, in this case obstetrics, pediatrics, and general medicine. Furthermore, this type of publication approach seemed apposite when endeavoring to answer speci c clinical questions in a eld with limited primary study. Finally, it was deemed that a traditional integrated review paper might be optimal when exploring a myriad range of health outcomes, both short and long term [6].

Clinical Relevance of Vitamin D Sufficiency in Reproductive Healthcare

e widespread clinical importance of determining the correlation between vitamin D levels and reproductive outcomes is evident.

e medical literature has achieved general consensus that vitamin D levels throughout much of the globe, as re ected by population measurements of 25(OH) D_3 levels, are generally inadequate. About 2/3 of the population in northern climates are considered de cient with average 25(OH)D3 levels in one study of 67 nmol/L, well below the 120-150 nmol/L level that has recently been associated with preferred health. With such widespread de ciency, it is vital to determine whether or not low gestational levels of vitamin D are a signi cant determinant of reproductive and pediatric health outcomes. e need for clarity on this issue has also been recognized because of disparity about recommended dosing among esteemed medical groups. While the Institute of Medicine (IOM) agrees that 4,000 IU of vitamin daily is allowable and nontoxic, their actual recommended daily intake has been limited to 600 IU daily in general and 400 IU/day during gestation.

ese IOM recommendations for required vitamin D intake have been put into serious question; however, as a signi cant statistical error has been identi ed in the way their recommendations were arrived. Accordingly, exploration of consensus ndings on the clinical bene ts of vitamin D supplementation is in order in all medical disciplines including reproductive healthcare [7].

Limitations of Vitamin D Research as Related to Gestational Outcomes

Although maternal-fetal outcomes in the presence of adequate gestational vitamin D are generally favorable as reported in the medical literature, some reports have been inconsistent and cast doubt on the link between gestational vitamin D su ciency and health. Speci cally, supplementation of vitamin D in pregnancy in some studies appears to suggest marked bene t while research in other publications does not appear to confer signi cant improvement in maternal-fetal outcomes. For example, a systematic review and meta-analysis by Perez-Lopez found that gestational vitamin D supplementation was associated with increased birth weight and birth length but, unlike some other research, was not associated with other bene cial maternal and neonatal outcomes such as reductions in preeclampsia, gestational diabetes, small for gestational age infants, preterm birth, or rates of cesarean delivery. e apparent disparity between ndings in various studies has caused some to re exively conclude that vitamin D status in pregnancy is irrelevant to maternal-fetal outcomes. Studies on reproductive outcomes related to vitamin D supplementation, however, are inherently plagued by a number of common confounders which cloud the picture. It is important to realize that vitamin D status is very di erent from whether or not someone is consuming vitamin D supplementation. Many factors may a ect the resultant status of vitamin D in the body (as re ected by measurement of 25(OH) D levels) a er ingested supplementation. Dosing of supplements, body weight, levels of various toxicants, and individual metabolism can all be factors in consequent vitamin D indices a er supplementation. Many of the recent publications challenging the e cacy of gestational vitamin D su ciency have been meta-analyses which attempt to synthesize diverse data from numerous observational and supplementation studies which do not necessarily incorporate individual di erences in these central determinants [8]. Speci c concerns about several vitamin D meta-analyses can account for the varying outcomes reported from this type of research. (i) ere is wide heterogeneity of studied populations with variations in vitamin D supplement dosing, geophysical location, social and dietary conditions, and other factors in studied groups. Supplementation at varying doses (e.g., 400 IU/day versus 4000 IU/day), for example, may achieve remarkably di erent levels of serum 25(OH) D and thus di erent outcomes. (ii) Commencement of supplementation at di ering times during the gestation may miss critical periods when vitamin D may play a pivotal role. (iii) Di erent types of vitamin D (vitamin D_2 versus vitamin D_3) have di erent physiological impact. And (iv) various methodological concerns are evident, such as the lack of standardized assays. In addition, it is well recognized in healthcare that regardless of how compelling the evidence on a speci c scienti c or medical issue, introduction of doubt can be a potent impediment to the implementation of e ective public health and clinical measures. Accordingly, a critical appraisal of such meta-analyses is in order to achieve an accurate perspective on the e cacy of

gestational vitamin D supplementation [9].

Gestational Vitamin D Status and Obstetrical Outcomes

e list of adverse gestational outcomes in pregnancy associated with vitamin D insu ciency continues to mount. Early in pregnancy, for example, an increased risk of rst trimester miscarriage has been linked to inadequate maternal vitamin D levels. Interestingly, one study demonstrated that nearly half the women assessed with habitual miscarriage were found to have 25(OH) D levels below 75 nmol/L.

is research found that lower vitamin D levels were associated with immune dysregulation in a number of ways, including di erences in indices involving natural killer cells, various cytokines, and certain regulatory proteins, when compared to those with su cient vitamin D levels. e authors of this study also noted that women with lower

for improved and enduring health and well-being associated with inexpensive measures to secure vitamin D nutritional adequacy during gestation, the most vulnerable time in the life cycle of the developing child.

Acknowledgement

None

Conflict of Interest

None

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