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ORIGINAL ARTICLE

Sex differences in dental caries experience: clinical evidence, complex etiology

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Abstract A sex difference in oral health has been widely documented through time and across cultures. Women's oral health declines more rapidly than men's with the onset of agriculture and the associated rise in fertility. The magnitude of this disparity in oral health by sex increases during ontogeny: from childhood, to adolescence, and through the reproductive years. Representative studies of sex differences in caries, tooth loss, and periodontal disease are critically reviewed. Surveys conducted in Hungary, India, and in an isolated traditional Brazilian sample provide additional support for a significant sex bias in dental caries, especially in mature adults. Compounding hormonal and reproductive factors, the sex difference in oral health in India appears to involve social and religious causes such as son preference, ritual fasting, and dietary restrictions during pregnancy. Like the sex difference in caries, tooth loss in women is greater than in men and has been linked to caries and parity. Results of genome wide association studies have found caries susceptible and caries protective loci that influence variation in taste, saliva, and enamel proteins, affecting the oral environment and the micro-structure of enamel. Genetic variation, some of which is X-linked, may partly explain how sex differences in oral health originate. A primary, but neglected, factor in explaining the sex differential in oral health is the complex and synergistic changes associated with female sex hormones, pregnancy, and women's reproductive life history. Caries etiology is complex and impacts understanding of the sex difference in oral health. Both biological (genetics, hormones, and reproductive history) and anthropological (behavioral) factors such culture-based division of labor and gender-based dietary preferences play a role.

Keywords Gender · Caries experience · Pregnancy · Reproduction · Sex hormones · Genome-wide scans

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Introduction

This paper examines evidence for sex[1] differences in oral health and emphasizes the important influence of reproductive and hormonal factors on women's oral health. A brief review of clinical and anthropological perspectives on sex differences in oral health is followed by a critical review of new clinical research on caries experience, tooth loss, and periodontal disease. New genetic evidence on caries susceptible loci is reviewed as potential mechanisms contributing to inter-sex differences in oral health and more specifically, predisposition to caries. The paper concludes with an emphasis on the critical significance that women's reproductive history and hormones play in explaining the so-called 'gender gap' in oral health [1].

In recent years, the biomedical community has developed an appreciation of fundamental and significant sex differences in patterns of health and disease [2]. The prime focus of sex differences in oral health centers on to the

[1] The terms 'sex' and 'gender' connote biological and cultural distinctions between females and males, respectively [61, 62]. Because this contribution focuses on the influence of basic sex-related biological factors on differences in caries experience and associated oral health factors, I have opted to use the term sex rather than gender in this contribution. Exceptions occur when directly referring to a publication that uses the term gender, as in the title "Using the DMF gender difference to assess the..." or the phrase '...the gender gap in oral health...' [1].

diverse consequences of pregnancy. Oral conditions commonly observed among pregnant women include gingivitis, granuloma, periodontal disease, erosion, caries, and tooth mobility [3–6]. The significant decline in oral health with pregnancy has an impact upon quality of life [7], and results from many complex and interacting variables, including genetic, behavioral, and hormonal factors [8]. The need for increased vigilance in monitoring and treating women's oral health during pregnancy is frequently expressed [3, 5, 6], yet dental care during pregnancy is an issue dominated more by caution and concern than by documentary evidence [9]. Adding new documentary evidence for sex differences in oral health as they relate to pregnancy is the goal of this paper. The perspective advanced here has direct relevance to clinical treatment of oral health in pregnant women, and provides additional baseline data for improving anthropological interpretation of dental disease in people of the past based on the analysis of prehistoric skeletal samples.

Anthropologists and bioarcheologists concerned with documenting health conditions and dietary patterns among prehistoric people have discovered a significant increase in dental caries through time, particularly in association with the origin and intensification of agriculture [10–13]. However, exceptions occur, for example in Southeast Asia [14], and importantly, not all cultigens are equally cariogenic. Inter-group differences in increasing caries experience with the origin of farming are also influenced by differences in food processing methods, contrasts in local micro-environmental, and ecological factors, and by population variation in the genetic foundations of enamel formation and micro-structure [15]. Sex differences in caries rates in prehistory were initially documented independently by different researchers in skeletal series in North America [16, 17] and in South Asia [18].

My interest in sex differences in oral health began in the early 1990s with insights gained from the analysis of the cemetery sample from the urban Bronze Age site of Harappa (5000 BP; Punjab Province, Pakistan) [13]. Subsequent analysis of dental pathology in early Holocene skeletal samples of nomadic hunters and foragers, associated with microlithic tools and lacking pottery, provided further evidence[19, 20]. The insight that women's oral health appeared to decline more rapidly than men's with the onset and intensification of agriculture prompted a search for etiological factors beyond the traditional anthropological 'behavior-based' consensus [21]. Clinical and experimental data revealed a general appreciation for the important role that pregnancy and hormones play in determining sex differences in oral health. Most of these influences on oral health are invisible to the bioarcheologist whose research focuses on pathological lesions in dry skeletons. Consequently, etiological agents associated with pregnancy, such as behavioral (more frequent eating), dietary (aversions and cravings), physiological (saliva flow and composition) and hormonal (high level of estrogen) factors, though important, were often overlooked or unappreciated by bioarcheologists. A meta-analysis of caries prevalence in prehistory, though limited by methodological constraints, showed the near ubiquitous pattern of inter-sex differences [22]. The cumulative impact of multiple pregnancies on oral health further exacerbates the sex difference in oral health, especially as fertility increases with the adoption of settled village life and the shift to farming [23]. One outcome of this study was the consistent and almost universal pattern in which women's caries experience significantly exceeds men's. In the following review of sex differences in oral health, I present a more integrative and holistic perspective in which the decline in women's oral health during pregnancy precipitates multiple interrelated and unfavorable oral changes, including caries, periodontal disease, and antemortem loss of teeth.

Clinical evidence

Gingivitis, bleeding gums, and associated tumors (epulis, granulomas) are the most frequently occurring and commonly discussed oral health problems of pregnancy [4, 6]. As uncomfortable and troubling as these symptoms are for pregnant women, they are ephemeral and reversible with the return to improved oral health post-partum. These soft tissue lesions are also invisible to the bioarcheologist conducting an analysis of oral lesions in archeologically derived human skeletal remains. By contrast, dental caries, periodontal disease, and tooth loss are oral lesions associated with pregnancy that are clearly discernable in prehistoric specimens and for which standards exist for scoring and recording [24–27]. The evidence in support of sex differences in caries experience, tooth loss, and periodontal disease are critically reviewed below, followed by a synthetic statement regarding the inter-dependence of their etiological relationship.

Sex differences in caries experience The age-dependent nature of caries experience is well established, as is the association of age and parity. In order to investigate sex differences in caries experience, data must come from large samples of adults, include values for both genders, and include age-stratified samples from early adulthood to old age. Concerns have been expressed regarding the comparative analysis of caries prevalence in prehistory [28], and many of these concerns are relevant when scrutinizing clinical or epidemiological data on dental caries. However, many investigators fail to report caries rates by gender, and abundant data is readily available by sex for children of

American and European heritage. By contrast, reports of caries experience among adults are rare generally and especially limited when anthropologically relevant, non-western populations of Africa, Asia, and South America are the focus of interest. A review of sex differences in a select global sample of clinical studies, showed a consistent pattern in which female caries experience was significantly greater than men's [23]. Here, additional documentation of sex differences in caries is presented, including two comprehensive surveys of large populations: one recently conducted in eastern Europe (Hungary; [29]) and one completed over 50 years ago in Asia (India; [30]). Results of an unpublished and ongoing meta-analysis of sex differences in caries rates in India and southwestern Asia are summarized along with results of a recent report on caries prevalence in an anthropological sample—a small indigenous mixed subsistence group of Brazil known as the Xavante [31].

In the Hungarian national survey a large sample size (2,923 women; 1,683 men) was distributed across six age categories (see Table 1), and data was collected by 'calibrated' dentists according to WHO [32] standards [29]. The goal of this cross-sectional dental survey was to generate new data on dental caries prevalence and tooth loss in different adult age groups in Hungary. While sex differences in caries prevalence are reported, temporal trends in tooth loss and caries prevalence are the main focus of this study. Table 1 was re-created from data presented in Tables 1 and 4 [in [29] and provides mean decayed, missing. and filled values (DMFT) by sex and one standard deviation. The authors state, in the abstract and the text, that "...caries prevalence was significantly higher in women compared to men *in all age groups* ($p<0.05$)." (emphasis added). Since sex differences in mean DMFT appeared small in some age groups, Student's t tests were conducted from summary data using SAS PC (ver. 9.2 for Windows; SAS Institute, Inc.), and resulting p values are presented in Table 1. Highly significant sex differences were detected in all age groups except the youngest (≤19 years) and oldest (≥75 years). This result contrasts with the findings reported by Madléna and colleagues [29]. However, the trends in inter-sex differences in caries prevalence are clear and easily appreciated in graphic form (Fig. 1). Error bars show one standard deviation about the mean DMFT value and were taken directly from Madléna ([29], Table 4). This bar chart clearly shows the increase in caries experience with age as well as the higher prevalence of caries among women, compared with men, in all age groups.

In his analysis of the 'gender gap' in oral health, Haugejorden [1] expressed the difference between genders in mean DMF values as a percentage of the weighted, pooled-sex mean. The mean percent gender difference for the pre-fluoride era (1946–1959) was 15.99 (min=0.0; max=40.93); across six age groups (12–17 years) with from four to six studies in each age group. In the post-fluoride era (1983–1993), the mean percent gender difference was 13.68 (min=−3.51; max=28.27); across six age groups (12–17 years), with from two to seven studies per age group. These figures provide context for the composite 12.4% gender difference computed for all ages of the Hungarian sample. The percent sex difference by age group is in the right hand column of Table 2, and ranges from a low of 4.95 in the oldest age group to a high of 25.36 in the 65–74 year age group. The increase in percent sex difference with age across adult age groups, from 20–35 years, to 65–74 years, reflects the progressively greater inter-sex difference in oral health with age, especially during and immediately following women's peak reproductive years.

Sex differences in caries experience were documented for a sample of age-matched men (n=417) and women (n=505) with similar social status from the city of Indore,

Table 1 Gender differences in mean DMFT in Hungary by age group

Age group (years)	Female			p^a	Male			Difference (%) combination mean[b]
	n	Mean DMFT	± SD		n	Mean DMFT	±SD	
≤19	38	12.34	7.14	0.3359	75	11.24	4.85	9.47
20–34	548	13.25[c]	5.65	0.0124	418	12.28	6.19	7.56
35–44	473	16.07[c]	5.16	0.0022	259	14.73	5.88	8.59
45–64	1,298	17.03[c]	6.87	<0.0001	647	14.07	7.56	18.45
65–74	416	24.81[c]	8.45	<0.0001	196	18.99	8.50	25.36
≥75	150	22.44	7.86	0.2856	88	21.35	7.09	4.95

Data from Madléna et al. 2009

[a] Probability computed using SAS PC from summary data in Madléna et al. 2009; Table 4

[b] Difference in mean DMFT (F-M)/gender pooled weighted mean

[c] Significant gender difference in mean DMFT

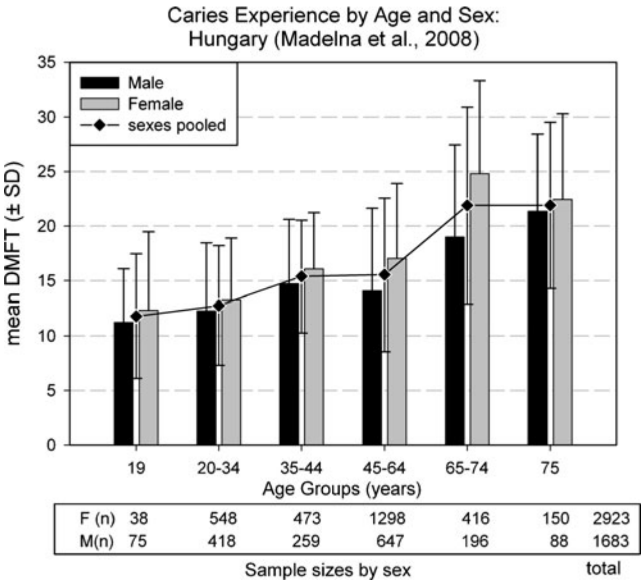

Fig. 1 Caries experience by age and sex: Hungary [29]

central India [30]. The goal of this study was to determine if a relationship exists between pregnancy and caries experience. Although no relationship was found, sex differences in caries experience are reported by age for five age groups and reveal a pattern similar to the Hungarian national survey. The analysis by Mangi [30] employed intra-oral examination with mirror and probe, with final diagnosis confirmed by X-ray, as required. Caries experience was reported using the percentage of carious teeth observed, not the more traditional method of DMFT. Though Mangi and colleagues [30] report sample size and percentage of carious teeth by gender, no statistical tests for significant differences in caries by sex were conducted. Using SAS PC (ver. 9.2 for Windows; Sas Institute, Inc.), I conducted chi-square tests for significant differences in the percentage of individuals with one or more caries by sex for each age group. Table 2 provides the percentage of carious teeth by sex for the Indore sample compiled from Mangi and colleagues [30], together with results of the chi-square tests. In all age groups, sex differences are significant (18–22 and 23–27 years) or highly significant (28–32, 33–37, and 38–45 years), with women's caries experience greater than men's. These results are graphically presented in Fig. 2, by sex and for the pooled sex sample. The sex gap in caries experience increases progressively and dramatically from young adult age groups (18–22 and 23–27 years) to older (28–32 years) and more mature adults (33–37 years). This study did not take tooth loss into account and the decline in caries experience in both genders in the oldest age group (38–45 years) may result from loss of teeth due to caries. The percent sex difference in frequency of carious teeth by age group is provided in the right hand column of Table 2, averages 69.44% with values gradually increasing from 34.46% among the youngest, to 106.17% in the oldest age group.

An extensive meta-analysis of over 50 clinical and epidemiological studies of caries experience in South Asia, primarily India, is nearing completion and will be published elsewhere [33]. A synopsis of the preliminary findings of this meta-analysis are: (a) in younger age groups mean DMFT (deciduous teeth) in males is greater than, or equal to, the female mean, (b) this pattern shifts from adolescence through maturity, including the reproductive years, during which most studies detect significant sex differences, with higher DMFT in females, (c) in many studies however no significant sex difference in caries is found. In addition to the negative influences of female sex hormones and changes in physiology and behavior associated with pregnancy, multiple social and religious factors may contribute to the sex difference in oral health in South Asia. These include the widespread practice of son preference/daughter neglect in patriarchal cultures [34], especially in north India; the practice of frequent fasting for personal and religious purposes among Hindu women [35], and the idea among pregnant women that a restricted diet ('eating down') will result in a smaller fetus

Table 2 Gender differences in caries experience in India (Indore, Madhya Pradesh)

Age group (years)	Female (n=505)		p[a]	Male (n=417)		Difference (%) combination mean[b]
	%	n		%	n	
18–22	2.55[c]	4,785	0.0375	1.76	2,326	34.46
23–27	2.55[c]	3,333	0.0174	1.62	2,401	43.01
28–32	3.28[c]	3,016	<0.0001	1.52	3,155	73.88
33–37	6.06[c]	1,006	<0.0001	2.60	1,768	89.70
38–45	5.08[c]	1,713	<0.0001	1.68	2,409	106.17

Data compiled from Mangi, 1954

[a] Chi-square probability computed using SAS PC from data in Mangi, 1954; Tables I–X

[b] Difference in mean DMFT (F-M)/gender pooled weighted mean

[c] Significant gender difference

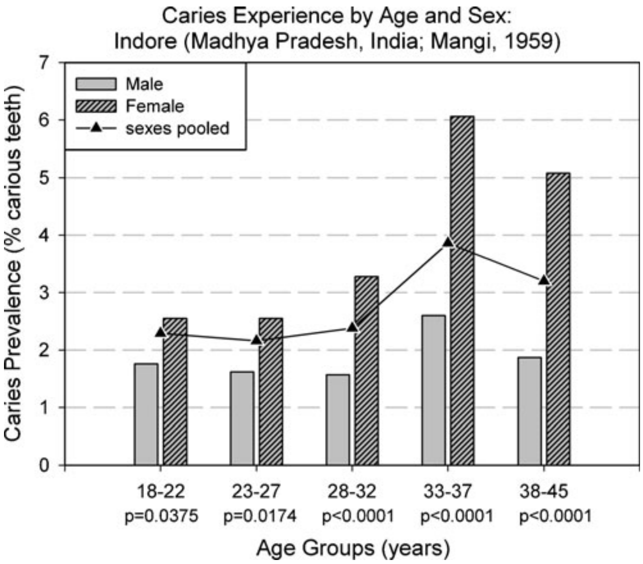

Fig. 2 Caries experience by age and sex: Indore (Madhya Pradesh, India; [30])

and easier childbirth [36: 147–149]. These socio-religious restrictions on diet may result in a sex bias in under-nutrition or malnutrition favoring women. These practices have the potential to enhance caries rates in women due to resulting changes in saliva flow rate and biochemical composition that result from repetitive acute (fasting) and chronic (under-nutrition and protein energy malnutrition) dietary restriction. Clinical, epidemiological, and experimental research has established an association between fasting, malnutrition, and changes in the oral environment that promote cariogenesis. Support for the relationship between childhood malnutrition and increased caries rates later in life come from studies in Lima, Peru [37], and from a review of the literature [38]. A controlled study found that fasting reduced saliva flow rate, increased rate of plaque formation, and changed concentration of phosphate and sialic acid in women [39]. Early childhood malnutrition results in salivary gland hypofunction that continues into adolescence [40]. These concepts are discussed in greater detail in my meta-analysis of the sex differential in oral health in India [33].

Anthropological populations, groups that are small, traditional, and practice a mix of foraging, hunting, and subsistence farming, are especially important as models for human health and nutrition in the recent past. Upon contact with outsiders in the 1940s, the Xavante, an indigenous group of central Brazil, shifted from reliance on hunting and collecting to increased dependence upon agriculture and sedentarization. A longitudinal analysis of dental caries, gender, and socio-economic change among the Xavante of Etenhiritipá village was recently completed by Arantes and colleagues [31]. Caries data were gathered by one investigator using WHO [32] standards. Intra-observer repeatability was high (Kappa coefficient=0.97) and caries experience by gender was reported by age using four age brackets. Mean DMFT for 1999, the baseline survey sample, are presented in Table 3, together with results of a Student's *t* test for significant gender differences in DMFT. In all age groups, mean DMFT is higher in women than men, but significant gender differences only occur in the 13–19 year old, and the 20–34 year old age groups. The gender difference is highly significant in the mature adults where the mean DMFT among females is more than twice the male mean. The gender difference in mean DMFT is clear in Fig. 3, which shows the absence of a gender gap in the youngest age group (6–12 years), a larger yet non-significant difference in the oldest—and most inclusive—age group (35–60 years) and large and significant gender differences in the middle two age groups: young and mature adults. The fertility rate for Xavante women between 15 and 40 years of age is 7.9 births [31], a potential contributing factor in the etiology of the significant gender gap in mean DMFT in mature adults.

Gender differences in Periodontal disease and Tooth loss Caries and periodontal disease are significant causes of antemortem tooth loss. The ubiquitous gender difference in caries, described above and elsewhere [23], is paralleled by patterns of tooth loss in which women typically exceed age-matched males. Higher frequencies of tooth loss among women have been documented in a diverse array of bioarchaeological and clinical studies. In skeletal samples, documentation of the gender difference in tooth loss comes from studies of the classic Maya of northern Petén [41], Iron Age Oman [42], medieval Japanese [43], and northwest Mexico [44], for example. As with the gender difference in caries experience, the female bias in tooth loss is not universal [45]. Clinical research documenting the greater rates of tooth loss among women include studies of permanent tooth loss in samples from Brazil [46], Chile [47], India [48], and Saudi Arabia [49]. Studies also show that among women, tooth loss is more often caused by caries, rather than periodontal disease [48, 50], and tooth loss increases in association with parity [50, 51]. These observations receive additional support from a longitudinal study of Danish twins that found a direct relationship between number of teeth a woman lost and number of pregnancies [52]. While the number of confounding variables make the etiology of tooth loss complex, it appears that parity remains a primary causal factor in tooth loss among women [51].

Genetic factors

Advances on several fronts are helping to clarify the mechanisms underlying gender differences in oral health: (a) variation in genes influencing enamel formation, (b)

Table 3 Mean DMFT by gender for Xavante (1999 baseline survey)

Age group (years)	Female			p^a	Male			Difference(%) combination mean[b]
	n	Mean	SD		*n*	Mean	SD	
6–12	38	0.66	1.28	0.7889	44	0.59	1.08	11.25
13–19	20	4.75*	4.62	0.0138	13	1.85	1.23	80.39
20–34	29	10.21*	6.44	0.0013	20	4.60	4.26	70.83
35–60	8	14.38	6.35	0.4900	12	12.50	5.50	14.19

Data from Arantes et al., 2009

[a] Probability computed using SAS PC from summary data in Arantes et al., 2009, Table II

[b] Difference in mean DMFT (F-M)/gender pooled weighted mean

[c] Significant gender difference in mean DMFT

genetic determinants of oral ecology, and (c) genomic diversity of oral bacteria. Genome-wide scans detecting associations between gene variants (quantitative trait loci) and every conceivable aspect of human variation have recently flourished and the number of publications are expected to peak in 2010 [53]. Not surprisingly, dental caries is among the diseases included in genome-wide association studies (GWAS). However, contrary to Miller's pessimistic disappointment in the accomplishments of GWAS research, the findings and implications for caries research hold promise. The first such study of 46 families from the Philippines found caries suggestive loci for genes influencing saliva flow and diet preferences [54]. The study documents a significant gender difference in mean DMFT between fathers (10.96) and mothers (14.45) in the Philippine families sampled [54]. A protective locus for caries was identified on the X chromosome (Xq27.1) and has implications for the global and widely reported gender differences in caries experience [21, 23]. Subsequent studies of variation in selected candidate genes involved in amelogenesis have focused on *ameloblastin, amelogenin, enamelin, tuftelin-1*, and *tuftelin interacting protein 11*, in a Guatemalan–Mayan sample [55] and in a sample of Turkish children [56]. Collectively, these studies suggest that variation in gene loci controlling enamel formation, especially *ameloblastin, amelogenin*, and *tuftelin*, contribute to observed differences in caries susceptibility. The authors hypothesize that genetic variation in these genes contributes to micro-structural alterations in enamel that may result in higher mineral loss under acidic conditions and may facilitate bacterial attachment to biofilms [56].

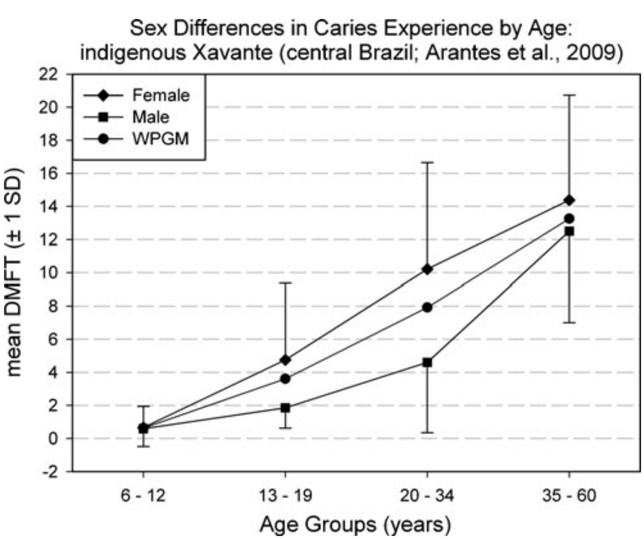

Fig. 3 Sex differences in caries experience by age; indigenous Xavante (central Brazil; [31])

Recent advances in genomic research have dramatically improved our view of caries microbiology by revealing the genome sequences of 15 different oral bacteria [57]. Understanding the genomics of plaque bacteria permits valuable insights into their evolution, physiology and regulatory mechanisms, some of which may be linked to virulence. Preliminary analyses of global diversity in the human salivary biome [58], coupled with advances in the ecology and succession of plaque microbial biofilms [59, 60] help to elucidate proximate mechanisms involved in individual and sex differential in caries etiology.

Discussion

Prior research in the field of bioarchaeology has documented a significant sex difference in oral health in past human populations, and across a diverse array of cultures and subsistence systems [11, 16–18, 22]. Clinical research reveals a similar and consistent sex differential in oral health, especially in caries experience in diverse global samples of living populations [1, 23]. The role that female sex hormones, pregnancy, and women's reproductive history play in contributing to the sex difference in oral health is supported by clinical research, but often unappreciated by anthropologists [21]. This report provides additional documentary evidence in support of the gender gap in oral health by reviewing the magnitude of the sex difference in dental caries experience and by describing the importance of the association between caries, tooth loss, and parity. A growing appreciation for the sex difference in oral health and the importance of women's reproductive history (total fertility) in contributing to differences in caries and tooth loss is encouraging [31, 44]. The multi-factorial and complex etiology of dental caries complicates analyses of the association between caries experience and pregnancy (parity). This results in contradictory and conflicting reports with a nearly equal balance of studies in support and against a causal linkage [see sources in 29]. Indirect evidence in support of a relationship between caries experience and parity comes from the widespread pattern in which the sex difference in caries and tooth loss increases with age, especially during women's reproductive years. Seeking evidence of a causal relationship between parity and poorer oral health in women will require greater care in research design that incorporates and controls for the diverse array of confounding variables, such as related oral lesions (periodonal disease and tooth loss), the details of women's reproductive histories, and contributing social and economic variables. Preliminary results of my meta-analysis of the sex disparity in dental caries in India exhibits the complex nature of confounding social and religious variables. These include son preference (daughter neglect) in health care and feeding regimens, the popularity of fasting as religious practice among Hindu women, and the belief that dietary restriction during pregnancy will result in a less difficult birth. These beliefs and behaviors take on added significance when coupled with clinical evidence that fasting, under-nutrition, and malnutrition result in changes in oral ecology promoting caries and in increased caries rates [37–40]. While social and religious factors such as these contribute to observed sex differences in caries experience, they are secondary to the impact of hormones and other systemic changes associated with pregnancy.

Finally, the results of genome-wide association studies hold promise for illuminating the causal mechanisms and pathways through which sex differences may in part originate. A significant aspect of the genetic studies is that the sex difference in caries experience may be caused by: (a) variation in the quality of tooth enamel (genes controlling enamel formation), (b) variation in oral ecology (saliva flow and composition), (c) variation in dietary preferences (olfaction and gustatory senses), and (d) variation in the pathogenic micro-organisms of the oral cavity. Clinical and epidemiological research into the sex differential in oral health needs to accommodate and control for as many contributing variables as possible. Future research into the sex bias in oral health holds promise for refining our understanding of the relative importance of the key variables that produce it (genes, physiology, pregnancy, and culture).

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Conflict of Interest The author declares that he has no conflict of interest.

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