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Expected prevalence of sheehan's syndrome in Mexico by extrapolation of screenings in other countries

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ABSTRACT

Background: Sheehan's syndrome (SS) occurs as result of ischemic pituitary necrosis due to postpartum hemorrhage; its prevalence in Mexico is unknown.

Objective: To estimate the approximate number of Mexican women that could have SS.

Methods: A search was performed in PubMed and Web of Science using the mesh terms: "postpartum hemorrhage" OR "Hypopituitarism". Besides these same keywords, in Google Scholar the search was expanded using the next terms: "Sheehan's syndrome prevalence". It was calculated the estimated cases of obstetric hemorrhage and the SS incidence in México based on casuistries from three countries.

Results: Extrapolating data from India, the total cases of SS in Mexico in the last five years could be as high as 322761 or about 2000 if taking Iceland's statistics. As the measure of all the adenohypophyseal hormones is of 56 dollars in Mexican public institutions, the option to make and early SS diagnosis should be to quantify only TSH that has a cost of 13.5 dollars.

Conclusions: The prevalence of SS in Mexico can have a 161-fold difference between the minimum and maximum values calculated by extrapolating information from other countries, so it is important to consider screening alternatives such as TSH measurement for its detection.

Keywords: Hypopituitarism; Postpartum hemorrhage; Sheehan's syndrome; TSH

INTRODUCTION

Sheehan's syndrome (SS) occurs as result of ischemic pituitary necrosis due to postpartum hemorrhage. Vasospasm, thrombosis, and vascular compression of pituitary arteries have also been described as possible causes. Even more, pituitary gland enlargement, small selar size, disseminated intravascular coagulation, and autoimmunity has been suggested to play a role in the pathogenesis of SS which has a wide spectrum in dysfunction degrees[1].

Some degree of hypopituitarism is present in almost one-third of patients with severe postpartum hemorrhage. In turn, although symptomatic posterior pituitary function is uncommon, many patients have alterations in neurohypophyseal function tests[2]. As such, SS may present in the postpartum period with lactatio-

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nal failure or many months or years after the birth that caused it. Evidence shows that, in many affected women, anterior pituitary dysfunction goes undiagnosed for many years[3].

Characteristic manifestations of SS include asthenia and weakness, dry skin, failure to lactate or resume menstruation, fine wrinkles around the eyes and lips, genital and axillary hair loss, premature aging signs, hypopigmentation and other evidence of hypopituitarism. Infrequently, it may present acutely with circulatory collapse, congestive heart failure, diabetes insipidus, hypoglycemia, severe hyponatremia, or psychosis[4,5].

In some studies it has been determined that the most common impairments are in growth hormone (GH) and prolactin secretion (90-100%), while deficiencies in cortisol, gonadotropin, and thyroid-stimulating hormone (TSH) secretion vary from 50-100%. It is known that for clinical manifestations to be evident, at least 75% of the pituitary must be destroyed[6,7]. Studies conducted so far, although limited in number, show that post obstetric hemorrhage hypopituitarism is a relatively rare condition in the developed world.

A study in Europe reported a prevalence of hypopituitarism of 45.5 per 1,000,000 and an incidence of 4.2 new cases per 1,000,000 person per year in 2001[8]. Massive postpartum hemorrhage is an important risk factor for the SS development. As early as 1939, Sheehan estimated that 41% of women who survived severe postpartum hemorrhage and/or hypovolemic shock had partial or severe hypopituitarism[9]. Improvements in obstetric care (such as early blood transfusion and/or administration of intravenous fluids) have considerably decreased the incidence of SS in developed countries[10,11]. However, due to the continued practice of home deliveries and poor healthcare structure in some primary care hospitals, SS remains a preventable cause of hypopituitarism[12]. The postpartum pituitary necrosis pathogenesis is not well understood. As a matter of fact, highly vascularized pituitary tissue is susceptible to ischemia even with relatively small changes in blood flow.[13] Thus, restricted pituitary blood flow when untreated and severe hypotension associated with obstetric hemorrhage is the common cause for the development of SS[13,14].

An enlarged pituitary gland, a small sella turcica, vasospasm, thrombosis, and coagulation abnormalities (acquired, as well as disseminated) are among the proposed predisposing factors for restricted pituitary blood supply[1].

As stated above, the main factor contributing to the SS etiopathogenesis is obstetric hemorrhage. According to the literature, the typical obstetric history of women with this syndrome includes massive uterine bleeding during or after delivery. In other words, massive postpartum obstetric hemorrhage may predict the SS development[15].

Severe postpartum hemorrhage is the result of uterine atony, allowing blood flow to continue to the placenta even after delivery. Many factors during pregnancy and delivery predispose to postpartum hemorrhage (advanced maternal age, anemia and obesity), but postpartum hemorrhage can occur despite the absence of these risk factors[16,17]. Postpartum hemorrhage is traditionally defined as blood loss of 500 ml after delivery or 1,000 ml after cesarean section in the first 24 hours; massive postpartum hemorrhage is the blood loss of ≥2,000 ml. Most pregnant women tolerate a blood loss of 1,000 ml, keeping a normal range of heart rate and blood pressure; the second begins to drop when the loss exceeds 1,500 ml[16–18].

Blood flow restriction at the level of the pituitary gland may be compromised due to arterial vasospasm when pharmacologic and nonpharmacologic management is not implemented as a priority[19]. In general, the pituitary gland becomes vulnerable to changes in blood flow during and shortly after pregnancy due to the increased size of the gland. This explains why hemorrhage and resulting hypovolemia during labor causes SS, whereas this is not the case if hypovolemia occurs from any other cause[18].

Lactational failure is a very common clinical feature and lack of prolactin response to thyrotropin-releasing hormone (TRH) administration has been suggested as a sensitive procedure for screening patients with suspected SS[20]. Patients with SS and central hypothyroidism have low free T3 (ft3) and free T4 (ft4), with paradoxically normal or mildly elevated serum TSH. However, they have severely attenuated TSH responses to acute TRH administration and no significant increase in serum TSH or ft4 levels after prolonged TRH infusion. This high TSH level is due to increased sialylation (a form of glycosylation), which reduces its metabolic clearance and leads

to an increased half-life[21,22].

TSH is the main regulator of thyroid function, it is a glycoprotein hormone composed of two non-covalently bound peptide subunits. The TSH subunits are glycosylated with mannose-rich oligosaccharides. After translation, they are combined and the bound oligosaccharides are further processed. Mature TSH molecules present complex structures of double-stranded and triple-stranded carbohydrates with reduced mannose content that are coated with sulfate and/or sialic acid[23,24].

Circulating TSH has multiple molecular forms or isoforms due to variations in oligosaccharide structures[25–27]. Furthermore, TSH isoforms have been shown to possess different biological activities, and both increased and decreased TSH bioactivities have been reported in various thyroid disorders[28,29]. The aim of the study was to estimate the approximate number of Mexican women that could have SS, suggesting TSH quantification as an initial screening to diagnose this syndrome.

METHODS

A search was performed in PubMed and Web of Science using the mesh terms: "postpartum hemorrhage" OR "Hypopituitarism". Besides these same keywords, in Google Scholar the search was expanded using the next terms: "Sheehan's syndrome prevalence" and “Prevalencia de síndrome de Sheehan en México”.

Inclusion criteria were cross-sectional studies, retrospective cohort, case reports, and official government documents to know the incidence of birth and SS. Exclusion criteria were articles that did not provide accurate, clear, and complete data.

Besides, an annual search was performed from 2016 - 2020 of the number of pregnancies in Mexico reported by the National Institute of Statistics, Geography and Informatics (INEGI), after which the cases of obstetric hemorrhages were estimated based on previous reports[28,29]. Finally, through the Excel program, the hypothetical SS prevalence was calculated extrapolating incidents from other countries[32-34].

RESULTS

According to the search criteria, 7 articles were registered (Table 1).

Table 1 - Analysis of Sheehan's syndrome data by country.

Study	Period	Type of study	Findings
Asaoka et al (Japan)[10]	1961-1970	Retrospective study of 1,010 women with a history of obstetric hemorrhage	No incidence of Sheehan's syndrome was found
Kristjandsdottir et al (Iceland)[32]	2009	Retrospective study in 100,000 women	Prevalence of 5.1 per 100,000 women
Zargar et al (India)[33]	2005	Population-based study	Sheehan's syndrome was diagnosed in 3.1% of patients over 20 years of age.
Tanriverdi et al (Turkey)[35]	2014	Retrospective study in 773 patients	Of the 773 patients, 27.6% were diagnosed with SS
Diri et al (Turkey)[36]	1960-2000	Cohort of patients diagnosed with hypopituitarism	114 patients were diagnosed with SS
Famuyiwa et al (Nigeria)[37]	1992	Observational study	Two cases of SS per year
Azeez et al (Nigeria)[38]	2016-2018	Case reports	Two to three SS cases per year

SS: Sheehan Syndrome

From these, a study from Japan, carried out from 1961 to 1970, in which 1010 patients with blood loss greater than 500 ml during delivery were selected and of the 392 patients who participated in the study, and SS was not confirmed in any of them.[10] A retrospective study in Iceland in 2009 of 100,000 women (mean age 37 years) found that only 8 of them were diagnosed with SS[32]. By contrast, in Kashmir, India, a study conducted in 2005 including 11,700 patients who suffered an obstetric hemorrhage and required transfusion, found that 98 of 8,730 multiparous patients aged 20-39 years and 51 of 2,970 multiparous patients over 40 years were diagnosed with SS, with the caveat that 63% of these patients gave birth in an out-of-hospital setting[33].

SS was the most common cause of hypopituitarism in women in Turkey, according to a study that analyzed 773 patients, in which the percentage of patients diagnosed with this syndrome was 27.6%, being more frequent in women older than 40 years (only 17% of diagnosed patients were younger than 40 years)[35]. Another retrospective study also performed in Turkey, showed that the number of patients diagnosed with this syndrome is inversely proportional to the number of deliveries attended at home, 25 of these patients were referred to the hospital for blood transfusion as a consequence of massive hemorrhage[36].

In Nigeria, two studies were conducted that yielded similar results. Famuyiwa et al. reported 11 cases over a 5-year period, giving a total of 2 cases per year[37], while at the University Teaching Hospital, five cases were reported over a 2-year period, giving a total of 2 to 3 cases per year. The mean age in the two studies was 35 to 37 years[38].

In Mexico, according to INEGI, in the period of five years, from 2016 to the year 2020, 10,411,707 pregnancies were counted; of which about 249,880 had obstetric hemorrhage and 52,058 had severe hemorrhages[39]. Table 2 shows the expected number of cases with SS in the last five years in Mexico, calculating it with the reported incidence from other countries.

Table 2 - Expected cases of Sheehan's syndrome in five years in Mexico

Year	**Pregnancies in Mexico[39] (n)**	**PPH cases in Mexico[30*] (n)**	**Severe PPH[31§] (n)**	**Extrapolated incidence based on:**		
				Iceland[32] (0.008)	**India[33] (0.031)**	**1 in 10000 deliveries[34] (0.0001)**
2016	2293708	55048.9	11468.5	440.3	71104	229.4
2017	2234039	53616.9	11170.1	428.9	69255.2	223.4
2018	2162535	51900.8	10812.6	415.2	67038.5	216.3
2019	2092214	50213.1	10461.0	401.7	64858.6	209.2
2020	1629211	39101.0	8146.0	312.8	50505.5	162.9
Total	10411707	249880.7	52058.2	1998.9	322761.8	1041.1

* Based on 2.4% of total pregnancies, § based on 0.5% of total pregnancies, PPH: post-partum hemorrhage

DISCUSSION

SS is a rare condition in developed countries, but in vulnerable areas such as India or South America, it remains a common condition[32]. In this sense and extrapolating the prevalence reported in other countries, the possible cases of SS in Mexico, at least in the last 5 years in the worst case would be more than 300,000 but unfortunately, no type of follow-up is done nor is there any recommendation to do a research in the risk group of women suffering from severe obstetric hemorrhage.

In addition to the complexity of finding a disease (SS) by finding when there is no institutional guide or indication to rule it out, it is added the fact that in a small percentage autoimmunity also plays a role in cases of hypopituitarism[40] and this condition is not sought for intentional way. Even more, several case reports exemplify the delay and confusion that the diagnosis of SS can lead to[41,42]. It cannot be omitted from mentioning that SS can be a cause of maternal mortality[43].

According to the literature, in as SS there are varying degrees of pituitary hormone deficiency after postpartum hemorrhage; however, the degree of hypopituitarism in SS is variable because in some cases there is partial or complete recovery of pituitary hormone[44].

The clinical manifestations of the syndrome depend on the degree of severity of the hormonal deficit. As a matter of fact, the secretion of growth hormone and prolactin is most commonly affected, followed by follicle-stimulating hormone and luteinizing hormone; severe necrosis of the pituitary gland also affects the secretion of thyroid-stimulating hormone and adrenocorticotropic hormone[45]. This means that, theoretically, the measure of all these hormones should be performed to discard SS in women with severe obstetric hemorrhage but here comes the question if it is feasible, and with a cost of 56 dollars in Mexican public institutions[46] would become a feat of spending for the majority of the women candidates because they live in poverty or extreme poverty[47]. Thus, the logical option to make an economically viable screening for the need to pay attention to a silent disease that must be afflicting thousands of women would be to quantify TSH levels in the first instance, since the cost is 13.5 dollars[48].

CONCLUSIONS

Obstetric hemorrhage in Mexico has been for several years the first cause of complications and death in Mexican pregnant women, so the prevalence of SS is latent in unconfirmed numbers, by making this survey, the prevalence of SS in Mexico can have a 161-fold difference between the minimum and maximum values calculated by extrapolating information from other countries, so it is important to consider screening alternatives such as TSH measurement for its detection.

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