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Original Research

Demographic, Clinical, and Obstetrical Characterization of Women with Hyperemesis Gravidarum Using a More Restrictive Diagnosis

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Abstract

Background: Hyperemesis gravidarum (HG) is a disease that occurs during pregnancy. It is relatively rare (0.3–3.6%), but with great potential for complications. Its diagnostic criteria still lack consensus, and most studies only establish the presence of uncontrollable vomiting, requiring hospitalization. The present study aimed to investigate its epidemiological profile and maternal and neonatal outcomes in a series of cases with more restrictive diagnostic criteria. **Methods**: A retrospective analysis of all cases admitted with a diagnosis of HG, according to more restrictive service criteria, was performed with a review of medical records and laboratory tests in a Brazilian university hospital. **Results**: HG was confirmed in 85 cases (0.39% incidence). The most frequent early symptoms included a weight loss $\geq$5% (94.4%) or $\geq$10% (63.9%), dehydration (76.5%), hyponatremia (49.4%), hypokalemia (40.5%), increased liver enzymes (46.4%), and transient hyperthyroidism (38.6%). Enteral nutrition was used in 7.1% of the patients, and parenteral nutrition in 1.2%. A large majority of patients was provided with a prescription of more than one drug, and the most used drugs were dimenhydrinate (87.1%), metoclopramide (85.9%), and ondansetron (38.8%). The average length of hospital stay was 15 days (1–145 days). Childbirth data were obtained from 40 patients, with 60% of births being cesarean deliveries, 35.3% premature births, 32% with low birth weight, and 7.5% stillbirths, with 12.5% of cases having postpartum complications. The overall rate for clinical complications was 30.5%. **Conclusions**: With well-defined and more restrictive criteria, we observed a high rate of obstetric and neonatal complications compared to international data. Thus, a correct diagnosis is essential for identifying this serious condition and to allow earlier treatment, reducing clinical, obstetric, and neonatal complications.

Keywords: hyperemesis gravidarum; pregnancy complications; pregnancy outcome; therapeutics; weight loss

1. Introduction

Although nausea and vomiting are common in pregnancy, with a frequency of 50–80%, usually limited to the first weeks of pregnancy and without significant clinical consequences, some pregnant women may have difficult-to-treat vomiting that continues beyond the first trimester, representing a condition of greater severity, but that is not clearly defined [1,2]. While some define severe nausea and vomiting during pregnancy as more than five daily episodes of vomiting or more than six hours of nausea per day, others define it as a loss of more than 5% of the pre-pregnancy weight, accompanied by ketonuria, that may or may not be accompanied by dehydration, and fluid and electrolyte imbalances or abnormal liver or thyroid function; such a condition has been referred to as hyperemesis gravidarum (HG) [2]. This disease affects a small proportion of the obstetric population, found usually in 0.3–3.6% of pregnant women, with a mean global incidence of 1.1% [3]. Despite its low frequency, HG may be the most common cause of hospitalization during the first half of pregnancy, with more than 59,000 hospitalizations per year in the United States, and the second most common cause of prenatal hospitalization throughout pregnancy, behind only preterm labor [2]. This infrequent condition is important due to its large clinical and obstetric consequences, requiring prolonged hospital stay and multi-professional treatment. The condition appears to be related to several maternal and neonatal complications, including significant weight loss, dehydration, nutritional deficiency, muscle weakness, Mallory-Weiss syndrome, Wernicke encephalopathy, fetal growth restriction, small-for-gestational-age (SGA) status, low birthweight (LBW), preterm delivery, and low Apgar score [4,5]. It is difficult for physicians to manage, because of difficulties in quantifying the severity of the disease and determining the best form of treatment, probably because the pathophysiology of the disease is not fully clear. However, despite its seriousness, few Brazilian studies have focused on this subject. We have identified only about a dozen Brazilian studies on the subject in the last 30 years, with only one epidemiological study, with a series of cases, specifically on aspects of HG during molar pregnancy [6]. None of the studies presented laboratory and clinical details or obstetric outcomes in a case series of patients.

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Considering the paucity of Brazilian data on this pathology, which can potentially lead to serious maternal and neonatal complications, and which lacks adequate treatment and a good description of its clinical and epidemiological features, we proposed to investigate the prevalence of the disease and its associated factors, clinical and laboratory profile, and obstetric and neonatal outcomes.

2. Materials and Methods

A descriptive and retrospective cohort study was conducted by surveying all cases classified as HG admitted to the Obstetric Clinic ward of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo, Brazil, between 2001 and 2015. Our hospital is one of the largest hospitals in Latin America, being a tertiary university hospital of reference for the entire southeastern region of Brazil, with approximately 12,000 obstetric outpatient visits, 5000 obstetric hospitalizations, and almost 2000 deliveries per year. The medical records were duly reviewed to confirm the diagnosis, excluding cases with underlying clinical pathology that ruled out the presence of HG, such as pancreatitis, appendicitis, hyperaldosteronism, diabetic ketoacidosis, and erosive gastritis. We defined HG as the presence of uncontrollable vomiting, with at least one of the following three criteria: significant weight loss (>5% pre-pregnancy weight), metabolic or fluid and electrolyte disorders, or dehydration, according to a protocol previously established in the service [7].

Several clinical, demographic, nutritional, laboratory, and disease evolution characteristics were analyzed, as were the main complications. Due to the rarity of the condition, a convenience sampling process was carried out.

The gestational age (GA) was calculated according to the last menstrual period, confirmed by either a first-trimester ultrasound or two second-trimester ultrasounds. The adequacy of birth weight for gestational age was classified according to the criteria of Alexander *et al*. [8].

The statistical analysis was descriptive, with measures of central tendency and dispersion, namely mean, median, and interquartile range (IQR) for continuous numerical variables and frequency for categorical variables. Statistical calculations were performed with the IBM SPSS 23 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

We analyzed 85 confirmed cases of HG during the study period, excluding cases with clinical disorders that may have led to misinterpreting the clinical picture. Considering the number of births that occurred during the period, with 21,742 births in 14 years, we calculated an incidence of HG of 0.39%.

3.1 Characterization of the Group

The 85 patients with confirmed hyperemesis were on average 25.8 years old (median = 25, IQR: 21–30), and the mean gestational age at the time of diagnosis was 13.2 weeks (median = 11.9; IQR: 9.9–14.7). Most were white (54.1%), in a stable relationship (32.9% cohabitating with their partners and 31.8% married), originated from the state of São Paulo (58.8%), with an educational level of up to complete secondary education (56.5%) and had received prenatal care in the same hospital (50.6%). Regarding occupation, most were housewives (44.7%); the remainder were students (7.1%) or worked in low-paying jobs, such as store clerks (4.7%). Concerning their obstetric history, for a little more than a third of the patients, it was their first pregnancy (36.5%), and almost half were nulliparous (44.7%), while almost one-fifth reported a previous miscarriage (18.8%). There was only one twin pregnancy (1.2%) and two cases of fetal malformation (2.3%). Six patients had data from two successive pregnancies, with recurrence of hyperemesis. A previous history of hyperemesis was observed in four other patients, totaling 10 patients with recurrent hyperemesis (11.8%).

From a nutritional point of view, the average pre-gestational body mass index (BMI) was 24.6 kg/m^2, with an IQR between 21.6 and 26.7, while the average BMI at admission was 21.9 kg/m^2, with an IQR between 18.5 and 23.8.

3.2 Initial Picture

With regard to the initial clinical picture, two-thirds of the patients (76.5%) presented with clinical signs of dehydration, and approximately one-fourth reported abdominal pain (27.1%) and being in good general condition (25.9%). Considering the difference between the weight at admission and the average weight of the patients before pregnancy, the average weight loss was 7.784 kg (approximately 12% pre-pregnancy weight, on average). Weight loss was $\geq$5% in 94.4% of cases; $\geq$10% in 64% of cases; and $\geq$20% in almost 10% of valid cases.

Compared to initial laboratory tests, approximately two-thirds of the patients had some laboratory alteration, as shown in Table 1.

3.3 Data on Hospitalization, Treatment, and Disease Progression

The 85 pregnant women were hospitalized on average for 15 days, ranging from 1 to 142 days, and in general had more than one hospitalization (range of 1 to 9 hospitalizations, with an average of 1.8). The weight gain between admission and delivery was on average 9.788 kg. Although this may seem appropriate, when considering the total weight gain throughout pregnancy and using the pre-pregnancy weight, it was observed that the weight gain was inadequate, with an average of only 2.594 kg (IQR: –4 to 9.3). Thus, many patients were unable to recover their pre-pregnancy weight.

As shown in Table 2, most of the patients were provided with intravenous hydration and electrolyte or vitamin

Table 1. Initial laboratory picture of 85 pregnant women with confirmed hyperemesis gravidarum.

Variable	Altered	Percentage of valid	Criterion
Anemia	11/80	13.7%	Hb <11 g/dL
Hyponatremia	39/79	49.3%	Na <135 mEq/L
Hypernatremia	1/79	1.3%	Na >145 mEq/L
Hypokalemia	32/79	40.5%	K <3.5 mEq/L
Hyperkalemia	1/79	1.3%	K >5.0 mEq/L
Abnormal Na/K	57/79	72.1%	Same as above
Hypocalcemia	4/40	10%	Ca_i <4.6 or Ca_T <8.6 mg/dL
Hypoalbuminemia	7/16	43.7%	Albumin <3.4 g/dL
Transient hyperthyroidism	17/44	38.6%	TSH <0.4 µm/mL
Hyperamylasemia	24/63	38.1%	Amylase >100 U/L
Hyperbilirubinemia	13/62	21%	TB >1.0 mg/dL
Increased Liver Enzymes	32/69	46.4%	ALT or AST >31 U/L

Hb, Hemoglobin; Na, Sodium; K, Potassium; Ca_i, Ionic calcium; Ca_T, Total Calcium; TSH, Thyroid Stimulating Hormone; TB, Total Bilirubin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

replacement therapy. Only 6 (7.1%) patients were provided with enteral nutrition, and only one (1.1%) was provided with parenteral nutrition. A large majority used more than one anti-emetic drug (mean of 2.7 drugs per patient). Notably, a large number of patients received anxiolytic or even antidepressant medication.

The rate of preexisting clinical complications was 23.5%, including the presence of the following conditions: urinary tract infection (6); depression (3); cardiomyopathy (2); chronic hypertension (2); syphilis (2); pyelonephritis (2); and other psychiatric disorders (3: schizophrenia, psychosis, and factitious disorder). Considering only complications directly related to HG, the rate of clinical complications was 7% (6/85), including the following conditions: prerenal acute kidney injury because of dehydration (3), and Mallory-Weiss syndrome (3). Overall, clinical complications occurred in 30.5% (26/85) of patients.

3.4 Childbirth: Obstetric and Neonatal Aspects

We evaluated the birth data of 40 patients. As shown in Table 3, the cesarean delivery rate was 60% and the median gestational age at delivery was 38.2 weeks. There were three stillbirths (7.5%), 12 babies (35.3%) were born prematurely (<37 weeks), and the low birth weight rate was 32.5%.

Five of these patients (5/40 = 12.5%) had postpartum complications, including acute anemia with coagulopathy, subaponeurotic hematoma with pulmonary thromboembolism, hematuria, hemorrhage with fever, and puerperal mastitis. One of these women was admitted to an intensive care unit.

4. Discussion

We conducted a study with a group of patients with a well-established diagnosis of HG [7], with a severity in general greater than that described in most studies, having considered only cases with hospitalization in which there was significant weight loss, dehydration, or fluid and electrolyte disorders. This definition encompasses only half of the cases initially included as HG and subsequently shown to be other pathologies or milder cases of vomiting of pregnancy. We believe that the current description of HG cases, with the more specific definition of the disease that is accepted by most Brazilian healthcare services, is useful for understanding how such a condition can affect maternal health. With this definition, we obtained an incidence of 0.39%, which is at the lower limit of the range found in the various studies on the subject. This value is similar, for example, with the incidence of 0.3% obtained by Källén [9], who surveyed the International Classification of Diseases code for HG in several hospitals in Sweden, with a variation between 0% and 1%. If we were to consider the hospitalization rate simply based on vomiting during pregnancy, a criterion used by many authors, our incidence would be 0.82%, a rate that is closer to the world average rate described by Einarson *et al.* [3] of 1.1%. We believe that our case review process, which excludes milder cases and those secondary to other causes, provides a more reliable description of the impact of the disease, which population studies have been unable to assess.

The demographic characteristics of our sample are partially comparable to those of most other studies. There was a predominance of young pregnant women (age <30 years: 71.8%), a rate similar to that reported by Dodds *et al.* [10], with 76.9% for women aged <30 years. Furthermore, our sample had a mean age (25.8 years) comparable with those reported in previous studies [4,11]. The number of non-white pregnant women (45.9%) in the present study is noteworthy, exhibiting by far the highest rate of all previous studies except one, in which 65.4% of patients were non-white; however, the study was specifically designed for a multiethnic population [4]. Fiaschi *et al.* [12], in Eng-

Table 2. Categorical variables of disease progression and treatment of 85 pregnant women with confirmed hyperemesis gravidarum.

Variable	Altered or Present	Percentage of valid
Intravenous hydration	84/85	98.8%
Electrolyte Replacement	41/84	48.8%
Enteral Nutrition	6/85	7.1%
Parenteral Nutrition	1/85	1.2%
Vitamin Replacement	23/81	28.4%
Dimenhydrinate	74/85	87.1%
Metoclopramide	73/85	85.9%
Ondansetron	33/85	38.8%
Ranitidine	6/85	7.1%
Anxiolytics	31/85	36.5%
Levomepromazine	26/84	31%
Chlorpromazine	6/84	7.1%
Diazepam	2/84	2.4%
Another anxiolytic drug	3/84	3.6%
Antidepressant	5/84	6%

Obstetric complications were observed in 28 women (33%), including the following, in order of numerical relevance: alteration of fetal vitality (7); fetal growth restriction (5); premature labor (4); short cervix/isthmus-cervical incompetence (4); vaginal bleeding (3 cases: one case of placenta previa and two of threatened abortion); pregnancy-specific hypertensive disease (2); premature rupture of membranes (2); and cord prolapse (1).

land, indicated that black women have a higher risk of HG compared to women of other ethnicities (odds ratio [OR] = 2.14). Similarly, Fejzo *et al.* [11], who evaluated women with severe vomiting in pregnancy recruited through a website (with 80% of Americans), observed among those with a more severe condition (weight loss >15%) a lower percentage of white women (78% vs. 88%) and a higher percentage of black women (3.3% vs. 2.2%), compared to women with less severe conditions.

Our nulliparity rate (44.7%) was also higher than the average rate of previously reported studies, with few studies describing higher rates than ours [10,12,13]. The mean gestational age at diagnosis (13.20 weeks) in the present study was also one of the highest in the literature, compatible with only one study (13.3 weeks) [14]. This may be related to the severity of our cases.

Another relevant finding, demonstrating the severity of our group of patients, was insufficient weight gain. Per the American Institute of Medicine recommendations [15], there should have been a weight gain of at least 11.5 kg if the patients had adequate pre-pregnancy BMI, which was the case for most of our patients, who had a previous mean BMI of 24.6 kg/m^2 and a BMI of 21.6 kg/m^2 at admission, which are in the eutrophic range. Thus, the average weight gain of 2.6 kg was at least a quarter of what it should have been. This fact may be related to the high rate of SGA newborns (22.5%), which is almost double the Brazilian rate [16]. Recent studies [17] also point to the importance of insufficient weight gain during the first two trimesters in its association with SGA newborns, a situation that occurred with most of our patients.

4.1 Laboratory Profile at Admission

Regarding the initial laboratory profile, we found a general condition of greater severity, with worse rates in most parameters in comparison with other authors, as shown in Table 4 (Ref. [11,13,18,19]).

Our rate of electrolyte changes was one of the highest in the literature. The rate of hypokalemia was the highest among all authors surveyed, while the rate of hyponatremia was surpassed only by data reported in a French study [19].

Regarding liver function tests, as shown in Table 4, our findings are similar to those of Chraïbi *et al.* [19], but are more severe than those of other authors. On the other hand, our rate of hyperbilirubinemia is the highest among all authors consulted [11,13]. Furthermore, Goodwin [20] established that mild liver enzyme elevations would be present in 20–30% of patients with HG, i.e., at rates lower than that found in the present study, which was 46.4%. Indeed, some authors have established a direct relationship between weight loss and liver changes [11]. The etiology of abnormal liver enzymes in HG is unclear. The liver enzymes return to normal levels promptly when vomiting ceases and adequate nutrition is resumed. It has been suggested that abnormal liver function is a combined effect of hypovolemia, malnutrition, and lactic acidosis that would occur in HG and may thus be related to the severity of HG [21]. This is in agreement with our finding of prerenal renal failure in 3.5% of cases.

The rate of anemia in the present study was similar to that reported in a Malaysian study [13], but more than double the rate reported in the French study [19]. However, our rate of anemia was lower than those described in an online study [11], both in patients with a milder condition (27.3%) and in those with a more severe condition (36.4%). However, these rates may refer to the final condition and not at the initial point.

The rates of transient hyperthyroidism (38.6%) found in the present study are relatively high, but are in agreement with those reported in several other studies in the literature. However, there are several different types of analysis used in the various studies, some distinguishing transient hypothyroidism and others encompassing all thyroid disorders. Some considered only TSH (Thyroid Stimulating Hormone) suppression, while others also considered the levels of free T4 and anti-thyroid antibodies. It should be noted for this comparative analysis that we excluded from our cases series four cases of pre-pregnancy hyperthyroidism or those with a diagnosis made during pregnancy that could explain the vomiting. This same methodological concern was not reported in any of the previously evaluated

Table 3. Descriptive variables of birth and newborn conditions of 40 patients with HG.

	N		Categories	N (%)	Median (IQR)
	Valid	Missing			
Type of Delivery	40	0	Cesarean	24/40 (60)	
			Forceps	3/40 (7.5)	
			Vaginal	13/40 (32.5)	
GA at delivery (weeks)	34	6			38.2 (35.8–39.7)
Prematurity (<37 weeks)	34	6		12 (35.3)	
Stillborn	40	0		3 (7.5)	
Sex Baby	39	1	Male	22 (56.4)	
			Female	17 (43.6)	
Newborn Weight (g)	40	0			2930 (2192.5–3317.5)
LBW Newborn	40	0		13 (32.5)	
Newborn Weight Classification	34	6	SGA	9 (22.5)	
			AGA	30 (75)	
			LGA	1 (2.5)	
NICU	36	4		4 (10)	
Apgar 1’	40	0			9 (8–9)
Apgar 5’	40	0			9 (9–10)
Apgar 10’	40	0			10 (9.25–10)
Apgar 1’ <7	40	0		7 (17.5)	
Apgar 5’ <7	40	0		4 (10)	

IQR, interquartile range; GA, Gestational age; LBW, Low Birth Weight (<2500 g); SGA, Small for Gestational Age; AGA, Adequate for Gestational Age; LGA, Large for Gestational Age; NICU, Neonatal Intensive Care Unit.

Table 4. Comparative laboratory of patients with HG data among several authors.

Author	Galletta, 2022 (current data)	Agmon 2019 [18]	Chraïbi 2015 [19]	Fejzo 2009 [11]	Tan 2007 [13]
Country	Brazil	Israel	France	EUA and others (on-line)	Malaysia
Number participants	85	89	109	214	166
Design	Retrospective	Retrospective	Retrospective	Cross sectional	Retrospective
Hyponatremia	49.4%		55%		37.6%
Hypokalemia	40.5%		16.8%		22.4%
Abnormal liver enzymes	46.4%		46.4%	6.5%	17.8%
Hyperbilirubinemia	21%		17.8%		11.3%
Transient hyperthyroidism	38.6%	2.2%	52.4%		55.2%
Hypoalbuminemia	43.7%				33.8%
Anemia	13.7%		6.6%	36.4%	14.5%

studies. In two of these studies [13,19], the excluded cases were described, and none were reported as being excluded due to thyroid disease. In any case, a review [20] indicated that transient hyperthyroidism occurs in 50–70% of women with HG. In a meta-analysis study [21], higher levels of free T4 and lower levels of TSH were described in patients with HG compared to controls.

4.2 Drug Treatment

As shown in Table 2, the treatment performed in the present study consisted mainly of intravenous hydration, with possible electrolyte replacement (in half of cases), in addition to antiemetic and anxiolytic drugs (in 36.5% of the cases). The most commonly used antiemetic was dimenhydrinate (87.1%), followed by metoclopramide (85.9%) and ondansetron (38.8%). This treatment regimen differs marginally from that of other authors. An American study reported that among the patients with milder and shorter-lasting symptoms, the treatments were distributed as follows: 55% seabands (wristbands that exert acupressure on the P6 Nei-Kuan point), 45% ondansetron, 41% promethazine, 38% antacids, 20% metoclopramide, 12% homeopathy, and 9% total parenteral nutrition. Among the most severe and longer-lasting cases, the treatment was slightly different: 72% seabands, 70% ondansetron, 66% promethazine, 56% antacids, 49% metoclopramide, 20% homeopathy, and 10% total parenteral nutrition [22].

The uncommon use of ondansetron in our sample is noteworthy, as it is a medication used in more than half of the patients in some series [11], and is known to be quite efficient in controlling symptoms [5]. It appears that there was some parsimony in its use due to a fear of using a newer

medication. Indeed, this is a genuine concern, because there is still some discussion in the medical literature about the safety of this drug. In fact, the safety of ondansetron has yet to be established. Recently, a meta-analysis [23] that studied 12 papers, concluded that there is an increased risk of ventricular septal defects (OR = 1.11) and cleft lip (OR = 1.22) and perhaps cleft palate (OR = 1.48). Although this perception of risk must be balanced against the increase in absolute risk, which still seems to be small [24], we understand that the use of this medication should be done with caution, reserving its prescription for more serious cases.

Furthermore, the rate of use of anxiolytics (36.5%) in the present study was extremely high, compared to Canadian data describing the use of anxiolytics in only 3.4% of pregnant women [25]. The use of antidepressants (6%) was also twice the rate described in an international systematic review study: 3.0% [26].

4.3 Enteral and Parenteral Nutrition

We used enteral nutrition 7.1% of the time and parenteral nutrition in only one case (1.2%). This is a very small rate given the severity of the cases. As a comparison, the rates described for parenteral nutrition in the United States vary between 15.9% and 35.1% and, for enteral nutrition, between 2.3% and 20.2% of cases of HG [11,27,28].

Furthermore, there are few reports in the medical literature on the use of parenteral or enteral feeding in HG. Holmgren *et al*. [28] described higher rates of the use of enteral nutrition (20.2%) and parenteral nutrition (35.1%) in their 94 pregnant women with HG, reporting fewer complications in enteral nutrition (tube displacement in 10.5%) and major complications in parenteral nutrition, with 66.4% having infection, thromboembolism, or both. Despite this, the enteral route was often rejected by the patients.

An interesting treatment protocol was established by a service in Norway [29], where there was a progressive evolution of conduct every three days if there was no improvement in intake or weight gain. With such procedures, high rates of the use of peripheral parenteral nutrition (31.72%) and enteral nutrition (19.17%) were described. Women with enteral nutrition exhibited greater weight loss at admission (mean of 5 kg) and at the beginning of treatment (mean of 5.5 kg) than the other groups (mean of 4 kg), representing a more severe condition. However, weight gain at the end of pregnancy was similar between the groups, demonstrating the effectiveness of this approach.

Thus, it seems reasonable that nutritional support should be initiated in women with HG who continue to lose weight and who do not respond to pharmacological and non-pharmacological treatments. The decision to initiate enteral or parenteral nutrition should be individualized, taking into account the gestational age, comorbidities, and preferences of the patient, as well as experience and institutional resources. In general, enteral nutrition is preferable, given the increased health risks associated with parenteral nutrition during pregnancy [5].

There appears to be a consensus that enteral feeding and total parenteral nutrition should be considered if intravenous therapy is not successful in reducing symptoms and there is still a caloric deficit.

Given such satisfactory results with enteral nutrition and considering the severity of our cases, with significant weight loss, we understand that we still have little use of this resource in our sample, maybe because we still have little experience. We believe that a similar situation exists for most Brazilian services and perhaps for many other services around the world. Therefore, the data presented here are of importance in the sense of alerting us to a change in our protocols. It would therefore be interesting to make greater use of this treatment option in the future, seeking better results.

4.4 Obstetric and Neonatal Characteristics

As can be seen from the analysis in Table 5 (Ref. [10,12,14,30–32]), the obstetric and neonatal results of our sample were more severe than those found by most international authors who investigated this topic.

Initially, 60% of the deliveries in our sample were cesarean, a rate higher than that of our tertiary service, which was approximately 45–50%, but also higher than that of all other authors. There are indications that the cesarean rate increases according to the severity of the HG case. Dodds *et al*. [10], analyzing 1270 women with HG in Nova Scotia, Canada, found higher cesarean rates among patients with a weight gain <7 kg than among other patients: 26.4% vs. 19.9%; OR = 1.4 (95% confidence interval [CI]: 1.0–1.8).

We also observed higher rates of premature birth, SGA, and low birth weight newborns in the sample, in addition to lower Apgar scores. Furthermore, we observed lower mean weight and gestational age at birth. Such rates could be related to the greater weight loss and lower weight gain observed in the sample. The study by Dodds *et al*. [10] demonstrates this association when comparing patients with HG with a weight gain <7 kg with other patients, noting an increased risk for LBW newborns, (12.5% vs. 3.4%, OR = 2.8), SGA (14.6% vs. 9.2%; OR = 1.5), prematurity (13.9% vs. 4.1%; OR = 3.0), and fifth minute Apgar <7 (5.6% vs. 0.6%; OR = 5.0). This association is reinforced by the data from Stokke *et al*. [29]. Norwegian patients hospitalized with HG who achieved a weight gain <7 kg had 20% LBW and 9% prematurity. Patients who achieved a weight gain ≥ 7 kg had 7% LBW and 5% prematurity (significant only for LBW). In the multivariate analysis, a weight gain <7 kg was the variable that attributed the highest risk for the LBW event. Authors such as Hastoy *et al*. [33] also observed an association between weight gain during pregnancy in women with HG and LBW. In a case-control study, they noted that when weight gain during pregnancy was <7 kg, there was a significant risk in HG patients compared to control patients for LBW (OR = 2.0; 1.0–3.1) and for fetal growth restriction (OR = 1.7; 1.1–2.4), but not for prematurity (OR = 1.6; 0.8–2.8).

Table 5. Comparison of the obstetric and neonatal results of the present study with other authors.

Author	Galletta, 2022 (current data)	Bailit, 2005 [14]	Dodds *et al*., 2006 [10]	Vikanes *et al*., 2013 [30]	Koudijs *et al*., 2016 [31]	Fiaschi *et al*., 2018 [12]	Gunay *et al*., 2020 [32]
Place	São Paulo Brasil	California EUA	Canada	Norway	Jakarta Indonesia	United Kingdom	Istanbul Turkey
n	40	2433	1270	814	354	83,679	186
C/S (%)	60	26.2	21.4		37.2	23.7	22
Stillborn (%)	7.5	0.71	0.5	0	3.7	0.4	0
Preterm birth (%)	35.3		6.5	5.3		4.9	8.1
LBW (%)	32.5	7.8	5.7	2.5	7.5	5.9	
SGA (%)	22.5	29.2	10.8	9.6	19.8	7.6	5.9
Apgar 5' <7 (%)	10		1.5	1.2			2.7
Male (%)	56.4		45.5		53.5	43	46.8
Birthweight (g)	2703 (mean) 2930 (median)	3255 (mean)		3602 (mean)	3116 (mean)		3250 (median)
Gestational Age (weeks)	36.71 (mean) 38.21 (median)	39 (mean)		39.85 (mean)	39.28 (median)		38.6 (median)

N, number; C/S, Cesarean Section; LBW, Low Birth Weight; SGA, Small for Gestational Age.

It is worth noting that 64% of our patients reported weight loss ≥10% and that the average weight gain rate during pregnancy was only 2.59 kg, with a median of 2.2 kg and an IQR between –4 kg and +9.2 kg. Such a picture is compatible with a significant risk for inadequate neonatal outcomes. In fact, in our data, the LBW rate doubled (42.9% vs. 21.4%) when weight loss was ≥10%, reinforcing the importance of such a large weight loss without satisfactory recovery in neonatal outcomes. Veenendaal *et al*. [34] established, in a systematic review with meta-analysis, that there is a higher risk in HG for low birth weight newborns, with rates of 6.4% in patients with HG and 5.0% in controls (OR = 1.42; 95% CI: 1.27–1.58). A similar risk was found in relation to preterm births, with rates of 7.4% in pregnancies with HG and 5.8% in normal pregnancies (OR = 1.32; 95% CI: 1.04–1.68).

The predominance of male fetuses (56.4%) observed in our sample was surprising, and is different from that observed in other studies. Schiff *et al*. [35], in a study with pregnant women hospitalized with HG in the US state of Washington, reported that the chances of these mothers of having a female baby were 50% higher than in healthy controls when the diagnosis of HG was made in the first trimester (OR = 1.5; 95% CI: 1.4–1.7), a risk that disappeared when the diagnosis was made later. As our average gestational age at diagnosis was 13.2 weeks, already later than the first trimester, this could partly explain the male predominance. Askling *et al*. [36] explained the predominance of female newborns by suggesting the possibility of female fetuses inducing greater amounts of beta-hCG (human chorionic gonadotropin). We speculate, therefore, that the cases in the present study may have had a lower hormone dosage, and that the clinical picture would not only be more severe, but it would also be explained depending on other causal factors. On the other hand, there does not appear to be any plausible evidence for hCG being associated with HG [1,2,5]. We look forward to new evidence of a genetic involvement in HG [37]. Perhaps the most severe cases are related to alterations in gene sequences and the milder cases are not. If so, this difference in fetal sex may be of importance in future investigations.

The high rates of inadequate neonatal outcomes, prematurity, SGA, and low birth weight found in the present study are possibly related to higher rates of fetal distress, low Apgar scores, greater use of neonatal ICUs, and higher perinatal mortality. Our neonatal intensive care unit utilization rate was relatively high, as seen in the comparison, for example, with data from Fiaschi *et al*. [12]: 10% vs. 1.6%.

Our stillbirth rate, 6.9%, was also very high, as can be seen in comparison with other studies. Hastoy *et al*. [33], for example, reported a 1.5% perinatal mortality, while Roseboom *et al*. [38] reported a 0.3% rate. Källén [9], in turn, reported a stillbirth rate of 0.47% and a neonatal mortality of 0.37%, that is, a perinatal mortality of 0.84%. At the other extreme, Vikanes *et al*. [30], in a Norwegian population-based study, described a zero perinatal mortality rate in their sample consisting of 814 pregnant women with HG.

Such results, which show worse rates than those of most other authors, may represent a more severe HG, probably related to the use of more restrictive diagnostic criteria of a well-established protocol, excluding dubious and less severe cases. In addition, we can consider that the treatment given to these women should have been better, more effective, and extensive, to ensure adequate weight gain and less maternal and perinatal repercussions. Thus, more restrictive diagnostic criteria may be useful to ensure a more accurate and early diagnosis of this condition, allowing more successful referral and treatment.

4.5 Limitations and Strengths

One of the strengths of this study is the fact that it is the first to survey a series of HG cases in Brazil, with a detailed description of laboratory, clinical, obstetric, and neonatal aspects. In addition, it advances the field by describing the findings based on more restrictive criteria, without considering only the presence of vomiting, but rather more compromised conditions, which would require hospitalization and multidisciplinary care. In this sense, the description of these cases leads to a series with one of the most severe HG characteristics in the literature, and serves to guide Brazilian obstetric services to best address these cases.

On the other hand, our study has some limitations and weaknesses.

Because the study was performed in a tertiary and university hospital, the possible presence of clinical and obstetric pathologies in these patients may have partially compromised the impact of obstetric and neonatal outcomes, which may be associated not only with HG, but also with these other pathologies. However, many of these diseases had already been excluded before the final analysis, as they could mimic HG-like conditions. Certainly, the inclusion of only 40 pregnant women with birth data is also a limitation of this study. There was a loss of approximately half of the cases hospitalized for HG, which compromises to some extent the assessment of perinatal outcomes. It possible that the patients who delivered elsewhere had good results and therefore did not return to our hospital, but this is just an assumption. In any case, the data we were able to obtain denote serious repercussions, and these are the only data on this topic currently available in Brazil. Finally, a larger sample would have led to a more robust comparative analysis.

5. Conclusions

We conclude that the present study is a pioneer in presenting clinical and obstetric data from a sample of patients with HG admitted to a Brazilian hospital, with well-defined diagnostic criteria, finding clinical and laboratory signs of worrisome severity. The rate of abnormal laboratory parameters and weight loss was higher than that of most other studies, indicating an apparently more serious condition. The same situation can be observed in relation to obstetric and neonatal outcomes, with clear severity, in relation to other international studies. In comparison with international protocols, the low use of enteral and parenteral nutrition is noteworthy, considering the severity of the sample. This panorama, possibly also shared with other Brazilian services, highlights the relevance of this condition and the importance of greater discussion among the specialists involved, to encourage not only correct diagnoses, but also a more effective treatment.

Author Contributions

MAKG—Conceptualization, project design and development, supervision of data collection, database analysis, statistical analysis, manuscript writing. MOD—Data collection, insertion in spreadsheets. ALTP—Conceptualization, project design and development, data collection. RPVF—Discussion of data, writing review, administrative support, Supervision. MZ—Administrative support, Supervision.

Ethics Approval and Consent to Participate

The procedures of the research were in accordance with the Helsinki Declaration and the project was approved by the Ethics Committee for Research Project Analysis (Comissão de Ética para Análise de Projetos de Pesquisa - CAPPESQ) of the Clinics Hospital of FMUSP in 2015 and was registered on Plataforma Brasil under the CAAE number 49631715.9.0000.0068. Because the research was retrospective, the hospital's research ethics committee agreed that the informed consent statement would not be applicable and accepted the release of this form. Care was taken to not identify the patients in the statistical spreadsheets, and the medical records were carefully handled.

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Conflict of Interest

The authors declare no conflict of interest.

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