ISSN 2218-6220 (online)

World Journal of

Obstetrics and Gynecology

World J Obstet Gynecol 2020 December 6; 9(1): 1-17

Published by Baishideng Publishing Group Inc

WJOG

World Journal of Obstetrics and Gynecology

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INDEXING/ABSTRACTING

World Journal of Obstetrics and Gynecology is now indexed in China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yun-Xiaojian Wu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

NAME OF JOURNAL
World Journal of Obstetrics and Gynecology

ISSN
ISSN 2218-6220 (online)

LAUNCH DATE
June 10, 2012

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
Simone Ferrero

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-6220/editorialboard.htm

PUBLICATION DATE
December 6, 2020

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ONLINE SUBMISSION
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World Journal of Obstetrics and Gynecology

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World J Obstet Gynecol 2020 December 6; 9(1): 1-10

DOI: 10.5317/wjog.v9.i1.1

ISSN 2218-6220 (online)

MINIREVIEWS

Myasthenia gravis and pregnancy

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Author contributions: Je G and Ghasemi M made contribution to the conception and design of the review paper's content and literature review; Je G wrote the initial draft of the paper; Ghasemi M and Je G critically reviewed, edited and finalized the paper for submission.

Conflict-of-interest statement: The authors declare no conflict of interest related to this work.

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Manuscript source: Unsolicited manuscript

Specialty type: Obstetrics and Gynecology

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Abstract

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular junction that has higher incidence in younger women than men, which could be related to differences in sex hormones physiology and immune system functioning between males and females. MG can first present during pregnancy and variably affect pregnancy, labor, and postpartum period. In this paper, we had an updated overview on our understanding about MG presentation and its effect on pregnancy and vice versa, therapeutic options for MG pregnant women, management of pregnancy or labor complications in MG patients, and finally fetal and neonatal considerations in MG pregnant women. A multidisciplinary approach, involving obstetricians/gynecologists, neurologists, and anesthesiologists, plays a pivotal role in improving the clinical outcomes in both MG mothers and their infants during pregnancy, delivery and postpartum.

Key Words: Pregnancy; Myasthenia gravis; Delivery; Postpartum; Transient neonatal myasthenia gravis; Pyridostigmine

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Core Tip: Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction that overall has higher incidence in women than men. This disease can variably affect pregnancy; and specific considerations need to be taken by a multidisciplinary team (including obstetricians/gynecologists, neurologists, and anesthesiologists) in pregnant women during their pregnancy, delivery, and postpartum period. We herein discuss about our understanding about MG presentation and its effect on pregnancy and vice versa, safe therapeutic approaches for MG as well as pregnancy/Labor complications, and finally specific fetal and neonatal considerations in MG pregnant women.

Citation: Je G, Ghasemi M. Myasthenia gravis and pregnancy. *World J Obstet Gynecol* 2020;

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 22, 2020
Peer-review started: May 22, 2020
First decision: October 6, 2020
Revised: November 9, 2020
Accepted: November 17, 2020
Article in press: November 17, 2020
Published online: December 6, 2020

P-Reviewer: Han GR
S-Editor: Zhang L
L-Editor: A
P-Editor: Li X

9(1): 1-10
URL: https://www.wjgnet.com/2218-6220/full/v9/i1/1.htm
DOI: https://dx.doi.org/10.5317/wjog.v9.i1.1

INTRODUCTION

Myasthenia gravis (MG) is one of the most common autoimmune neuromuscular junction disorders with a prevalence of about 200 per one million worldwide[1]. The characteristic clinical feature of MG is a fluctuating and fatigable skeletal muscle weakness. The most common initial presentation is ocular weakness with asymmetric ptosis and binocular diplopia, and less commonly early or isolated oropharyngeal or limb weakness[2]. The underlying pathophysiology is mostly related to production of autoantibodies against the acetylcholine receptors (AChRs) or other related protein complexes on the postsynaptic muscle membrane such as muscle specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related protein 4[1]. Additionally, pathologic thymic involvement including thymoma is present in 10%-20% of MG cases, particularly those with anti-AChR autoantibodies[2]. Women younger than 40 years old are more frequently affected than men with the same age range, with a female/male ratio of 3:1 for AChR MG and 9:1 for MuSK MG[3]. MG status during pregnancy is overall considered as unpredictable. Little is known about the underlying pathophysiology and etiology of unpredictable complications during pregnancy and the post-partum period, though some evidence suggests a role for sex hormones[4,5]. In this review, we discuss clinical presentation of MG during pregnancy, its effect on pregnant women and their children, pre-pregnancy planning in MG women, therapeutic options during pregnancy and breastfeeding, as well as considerations that need to be taken when managing pregnancy or delivery complications in MG patients.

HORMONAL EFFECTS ON MG

Sex hormones, especially estrogen but also progesterone as well as testosterone, are known to affect immune system[6]. MG which is one of the autoimmune diseases commonly affects women than men, especially childbearing age, indicating a role for sex hormones on MG.

Several previous studies have demonstrated that sex hormones have effects on modulating disease severity of MG[4,7], particularly during the menstrual period and pregnancy. MG symptoms are frequently exacerbated before and during the menstrual period[8] but opposite cases were also reported[9]. In addition, exacerbation of MG symptoms can occur during pregnancy[10,11]. Even though available studies indicate that sex hormones can influence immune system and modulate disease severity of MG, further studies are needed to confirm the underlying mechanisms.

MG AND PREGNANCY

MG symptoms can be first developed during the pregnancy or postpartum period[12,13]. In rare cases, myasthenic crisis can be the first symptoms to seek medical attention during pregnancy[14].

Appropriate diagnosis and treatment are important to avoid further exacerbation especially during pregnancy. Anti-AChR, -MuSK or - low-density lipoprotein receptor-related protein 4 antibodies can be tested to confirm the diagnosis of MG during pregnancy. If the results of these tests are negative, electrodiagnostic studies including repetitive nerve stimulation or single-fiber electromyography can be used as safe diagnostic tools during pregnancy. Chest computerized tomography (CT) to look for thymoma can be delayed until after the delivery to avoid unnecessary radiation exposure since there will be no expected benefit from thymectomy during pregnancy[15] and the incidence of thymoma in young MG patients under age 30 s is low[16,17]. If thymoma is strongly suspected, mediastinal magnetic resonance imaging will be preferred than chest CT.

MG by itself does not have much influence on pregnancy including duration of pregnancy, risk of miscarriage or birth weight[18,19]. The course of MG disease during pregnancy is overall unpredictable. Exacerbation of MG symptoms can occur in about

one third of pregnant women, especially in the first trimester and also postpartum period but the long-term course of MG is not worsened by pregnancy[10,11]. In addition, disease course of MG during pregnancy cannot be predicted by disease severity at the time of pregnancy and also previous course of pregnancy on MG[10]. For these reasons, pregnant women with MG should be seen by their obstetricians and neurologists relatively frequently throughout their pregnancy. They also need to be instructed to monitor fetal body movements carefully and get immediate medical advice if they feel reduced fetal movements. Pregnancy can change total blood volume, gastrointestinal absorption as well as renal clearance. Therefore, further medication dose adjustment may be needed during pregnancy. An overview of previous studies of MG in pregnancy are summarized in Table 1.

PRE-PREGNANCY COUNSELLING IN MG WOMEN

Women with MG who are in childbearing age should be encouraged to discuss their plan for pregnancy with their neurologists in advance. Optimizing the treatment before and during pregnancy is the key for the safe pregnancy and a multidisciplinary team approach consisting of the patient, her partner and family, a neurologist as well as an obstetrician is required in this condition[15,20]. If the patient is recently diagnosed with MG, delaying her pregnancy at least one to two years may be recommended to estimate her disease severity and optimize the individual therapy.

The treatment of MG includes medications for symptomatic relief such as cholinesterase inhibitors and immunosuppressants such as steroids, azathioprine, cyclosporine, mycophenolate, cyclophosphamide, methotrexate as well as intravenous immunoglobulins (IVIG) and plasmapheresis. Some of the medications can be continued safely during pregnancy and breastfeeding. Among those, oral pyridostigmine is considered as the first-line treatment[12,19]; however, intravenous cholinesterase inhibitors should not be used during pregnancy since they can induce uterine contractions[15]. Patients with insufficient control of MG symptoms with pyridostigmine require immunosuppressants. Among immunomodulatory medications, steroids are the treatment of choice in pregnancy as their adverse effects to myasthenic mother or fetus are minimal except for slightly increased risk of cleft palate, infection, weight gain, gestational diabetes and preterm delivery[21-23]. Immunosuppressants other than steroids are mostly avoided during pregnancy, but azathioprine and cyclosporine can be used as steroid-sparing agents if required. Even though a number of studies have reported increased risk of intrauterine growth retardation, prematurity and low birth weight, there is no association between fetal malformations and azathioprine or cyclosporine exposure during pregnancy[24,25]. Mycophenolate, cyclophosphamide and methotrexate are considered as teratogens and they are contraindicated during pregnancy[26-28]. There is limited data on rituximab and eculizumab use in pregnancy. Rituximab can decrease B-cell and $CD19^+$-cell counts in newborns transiently[29] and increase the risk of prematurity as well as low birth weight[30], but the recent report has shown healthy baby deliveries from myasthenic mothers who were on rituximab[31]. Eculizumab was approved by food and drug administration for treatment of MG recently, thus its effect on pregnant women with MG is still elusive. Notably, there are several previous studies which have shown safe use of eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome[32-34]. Table 2 summaries current treatment options in MG during pregnancy.

Thymectomy can improve clinical outcomes and reduce use of immunosuppressants in MG patients[15]. While it is recommended for patients especially who have thymic hyperplasia or thymoma, it should be delayed until after delivery if patients are pregnant since expected benefits from thymectomy during pregnancy is very low[15,35].

MANAGEMENT OF COMPLICATIONS DURING PREGNANCY IN MG PATIENTS

It is important to monitor and treat exacerbation of MG or myasthenic crisis during pregnancy. Hypoventilation related to elevation of diaphragm, infections, fatigue and stress are major causes of exacerbation of MG during pregnancy. IVIG or plasmapheresis along with supportive care may be used safely in pregnancy and they

Table 1 Summary of previous studies of myasthenia gravis in pregnancy

Ref.	Number of pregnancies/patients	Treatment	MG during pregnancy	Mode of birth	TNMG	MG after birth	Other findings
Plauché[60], 1991	322/255	NA	41.0% exacerbation, 31.7% no change, 28.6 % remission	5.6% C-sec before 1963; 15.4% forceps, 13.5% C-sec after 1963	14.9%	29.8% exacerbation, 4 % death	Large literature review
Batocchi *et al*[10], 1999	64/47	42 underwent thymectomy before conception 36% on no treatment, 47% on pyridostigmine alone, 17 % on multi-treatments (pyridostigmine, steroids, azathioprine, IVIG or plasmapheresis)	17% relapsed (no treatment); 19% relapsed, 42% unchanged, 39% improved (on treatment)	30% C-sec (most for obstetric reasons)	9%	28% worse	No correlation between TNMG and maternal disease severity
Djelmis *et al*[11], 2002	69/65	23.2% on no treatment, 43.5% on pyridostigmine alone, 33.3 % on pyridostigmine and steroids 9 received plasmapheresis	14.5% exacerbation, 22.3% unchanged, 24.6% improved	8.7% vacuum extraction, 17.4 % C-sec	30.0%	15.9% exacerbation	Inverse association between incidence of TNMG and maternal disease duration
Hoff *et al*[42], 2003	127/79	45 underwent thymectomy (16 before the first conception), No record before 1999; 54.5% on pyridostigmine alone since 1999	NA	17.3% C-sec, 8.7% forceps/vacuum extraction	3.9%	NA	Three times higher risk of preterm rupture of amniotic membranes in MG
Hoff *et al*[62], 2004	49/37	6 underwent thymectomy before conception	29.7% remission	14.6% C-sec, 8.2% forceps/vacuum	NA	NA	6.1% neonatal mortality. No correlation between TNMG and maternal disease severity
Hoff *et al*[12], 2007	135/73	50% on treatment at the time of conception (99% on pyridostigmine, 1% on steroids), then 45% continued throughout pregnancy, 3 received plasmapheresis	10% relapsed	19% protracted labor	19%	NA	A half risk of TNMG if mother had thymectomy
Wen *et al*[43], 2009	163/163	NA	NA	44.8% C-sec	NA	NA	No significant difference in the risk of preterm, low birth weight, small for gestational age and C-sec between women with and without MG
Almeida *et al*[14], 2010	17/17 (2 abortion)	23.5% on no treatment, 5.9% on pyridostigmine alone, 5.9% on steroids alone, 5.9% on IVIG alone, 47% on multi-treatments (pyridostigmine, steroids or IVIG)	23.5 % relapsed, 47.1% unchanged	47% C-sec (most for obstetric reasons)	NA	17.6% MG crisis	C-sec only carried out if there are obstetric reasons on women with controlled MG
Ducci *et al*[44], 2017	35/21 (4 abortion)	5 underwent thymectomy before conception, 8.6% on no treatment, 91.4% on treatment (22.9% on pyridostigmine alone, 68.6% on multi-treatments) at the time of first trimester, then most of them continued throughout pregnancy	50% relapsed, 20% unchanged, 30% improved	66.7% C-sec, 6.7% forceps/vacuum	12.9 %	NA	Severity and duration of MG, repetitive nerve stimulation and treatment influence MG and pregnancy
Gamez *et al*[63], 2017	5/5	100% on monthly IVIG (switched to IVIG prior to pregnancy)	100% unchanged	60% C-sec	0 %	100% unchanged	IVIG monotherapy during pregnancy in MG women could be a good option but bigger study is required
Santos *et al*[64], 2018	27/13 (All MuSK MG, 4/4 for pregnancy after MG onset)	77.8% on no treatment (74.1% who was pregnant before MG onset), 7.4% on pyridostigmine and steroids, 7.4% on multi-treatments including pyridostigmine and steroids with azathioprine or IVIG	3.7 % relapsed	22.2% C-sec	3.7%	0% relapse	Pregnancy does not precipitate MuSK MG

MG: Myasthenia gravis; IVIG: Intravenous immunoglobulins; MuSK: Muscle specific tyrosine kinase; TNMG: Transient neonatal myasthenia gravis.

are generally well-tolerated[36,37].

Preeclampsia, eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) are potentially life-threatening complications of pregnancy which require prompt therapy urgently. MG does not have any effect on these pregnancy complications; however, there are some important considerations in management of these complications in MG women. Certain medications (β-blockers and calcium channel blockers) should be avoided for blood pressure control since they have the potential to exacerbate MG symptoms or crisis. Methyldopa or hydralazine are considered as drugs of choice[38]. For seizure prophylaxis, magnesium sulfate should be avoided since it can block acetylcholine release and interfere neuromuscular transmission[15,39]. Barbiturates or phenytoin can be considered as alternative therapy instead of magnesium[15]. If β-blockers, calcium channel blockers or magnesium sulfate are needed, close monitoring is essential for the patient care. For HELLP syndrome, heparin, aspirin, plasmapheresis or IVIG can be used in addition to proper blood pressure management and seizure prophylaxis[40,41].

CONSIDERATIONS DURING LABOR AND BIRTH

Maternal MG has an increased risk for birth complications, most commonly preterm rupture of membranes, even though MG by itself does not increase the risk for pregnancy complications including spontaneous abortion or premature birth[42-44]. Vaginal delivery should be always encouraged in women with MG and cesarean delivery should only be performed for standard obstetric indications[15]. MG does not affect the first stage of labor since the uterus which is composed of smooth muscle is not affected by the disease due to lack of the postsynaptic AChRs. However, the second stage of labor may get affected since the striated muscle is involved during expulsive efforts and it can result in maternal fatigue. Forceps or vacuum extraction may be required to ease this stage of labor[11,39] and an increased cesarean delivery rate was also reported due to maternal fatigue during the labor[42]. Parenteral cholinesterase inhibitors can be used to strengthen muscles during labor and stress dose of intravenous hydrocortisone (100 mg) is recommended to patients who are on chronic oral steroids (at dose larger than the equivalent of 7.5 mg/d prednisone) during the intrapartum period[20,43,44].

Epidural analgesia is the most preferable method during labor and regional anesthesia is recommended for cesarean delivery[14,45]. General anesthesia and neuromuscular blocking agents should be avoided if possible. Sedatives and opioids should be avoided as well since they can possibly induce respiratory depression. If they are unavoidable, patients should be monitored carefully with a peripheral nerve

Table 2 Treatment options in myasthenia gravis during pregnancy

Medication	FDA category	Effects on pregnancy	Breastfeeding
Treatment of choice			
Pyridostigmine	B	None reported	No limitation (Excreted in breast milk)
Steroid	C	Cleft lip or palate (rare), low birth weight	No limitation (Excreted in breast milk)
Treatment of choice for steroid-sparing agents if indicated			
Azathioprine	D	Intrauterine growth retardation, prematurity, low birth weight, hematological toxicities (lymphopenia, pancytopenia) in newborn	Limited but can be considered (Excreted in breast milk)
Cyclosporine	C	Intrauterine growth retardation, prematurity, low birth weight	Limited but can be considered (Excreted in breast milk)
Contraindicated			
Mycophenolate	D	Congenital anomalies	Contraindicated
Cyclophosphamide	D	Congenital anomalies	Contraindicated
Methotrexate	X	Fetal death, congenital anomalies	Contraindicated
Insufficient data			
Rituximab	C	Transient B- and CD19+-cell depletion in newborns, prematurity, low birth weight	Limited data (minimally detected in breast milk)
Eculizumab	C	Limited data (prematurity)	Limited data (not detected in breast milk)
Treatment of choice for exacerbation of MG or myasthenic crisis			
IVIG	C	None reported	No limitation
Plasmapheresis	N/A	Small for gestational age	No limitation

FDA: Food and Drug Administration; MG: Myasthenia gravis; IVIG: Intravenous immunoglobulins.

stimulator[20].

FETAL AND NEONATAL CONSIDERATIONS

Maternal AChR antibodies can be transferred to the fetus, which can cause transient neonatal myasthenia gravis (TNMG) in about 20% of infants who are born to myasthenic mothers[46]. Symptoms are noticeable with general muscle weakness, poor sucking, weak cry, swallowing difficulty, lethargy and breathing difficulty. In most cases, these symptoms present within few hours to three days after birth. Therefore, all infants from myasthenic mothers should be monitored closely, especially in the first few days[47]. Most infants with TNMG have myasthenic mothers with active disease; however, some mothers may be in remission or may not have any evidence of MG. In addition, there is no clear correlation between maternal disease severity as well as maternal antibody titers and existence of TNMG[48,49].

TNMG should be suspected in the symptomatic infants born to mothers with history of MG. Diagnosis can be made with elevated levels of anti-AChR or anti-MuSK antibodies, decremental response in repetitive nerve stimulation or clinical improvement after administration of cholinesterase inhibitors in symptomatic infants. Neostigmine is the most commonly used cholinesterase inhibitors as a diagnostic bedside test[49]. Treatment usually depends on severity of TNMG. For mild symptoms, supportive care with small amount of feeding or nasogastric feeding, ventilatory support and/or cholinesterase inhibitors are sufficient. For more severe cases, IVIG or plasmapheresis needs to be considered[20,49]. Overall, TNMG has good prognosis if it is early identified and properly treated. Symptoms usually resolve in the first two months but can last as long as 4 mo[50].

There is rare but more severe manifestation reported in infants born to myasthenic mothers including arthrogryposis multiplex congenita[51]. Arthrogryposis multiplex

congenita can be a potentially fatal condition resulting from decreased limb movements, for which pregnant women with MG should be advised and encouraged to monitor their fetal movements and get fetal scan at 13 and 20 wk of pregnancy[20,51].

BREASTFEEDING

Breastfeeding after delivery is not a contraindication in women with MG, if their disease is well-controlled[20]. On the other hand, breastfeeding should not be considered if their disease is poorly-controlled since increased fatigue associated with nursing may increase the likelihood of disease exacerbation. Breastfeeding does not increase the risk of myasthenic symptoms in newborns, even though maternal IgG are known to present in breast milk[52].

In terms of therapy, there are few relatively safe therapies during breastfeeding including cholinesterase inhibitors, steroids and IVIGs[15,20,52]. Although cholinesterase inhibitors are detected in the breast milk, they are considered safe since their levels are relatively low in the breast milk unless patients require high doses[53]. Azathioprine and cyclosporine are acceptable during breastfeeding[54,55], whereas mycophenolate, cyclophosphamide or methotrexate should be avoided since they are excreted in breast milk and affect the newborns[56,57]. There are very few studies available for the effects of monoclonal antibodies including rituximab and eculizumab on breastfeeding, which have shown very minimal effects without any significant harm[58,59].

CONCLUSION

MG may first manifest during pregnancy and can variably affect pregnancy and labor period in an unpredictable manner. Overall, worsening of MG symptoms (*i.e.*, MG crisis) occurs more commonly in the first trimester or in the first month postpartum. Even, effects of pregnancy on MG may vary in subsequent pregnancies in a patient with MG[60-64]. Therefore, close monitoring of MG women during their childbearing age is crucial. On the other hand, given the unpredictability of MG course during pregnancy, we would recommend that the MG patients to be frequently evaluated during and before pregnancy because this can help physicians to timely and appropriately modify the MG therapy based on alterations in the disease severity. It is also noteworthy that the treatment options for MG are limited in pregnant or breastfeeding women compared to other MG patient population. Based on our clinical experience and previous studies, a considerable number of MG patients can safely benefit from oral pyridostigmine alone or in combination with steroid therapy (*e.g.*, oral prednisone) during pregnancy. However, if more aggressive immunosuppressive therapy is needed (*e.g.*, due to intolerance or insufficient response to pyridostigmine or steroid therapy), azathioprine and cyclosporine can be considered as steroid-sparing medications. Knowing the side effect profile of immunosuppressive medications in pregnant women and their fetus is essential, as some of these medications such as mycophenolate, cyclophosphamide and methotrexate are contraindicated in these patients due to teratogenicity. Overall, we preferably discontinue immunosuppressants 4 to 6 mo before conceiving. Additionally, IVIG, plasmapheresis, and corticosteroids are usually preserved for myasthenic crisis when more immediate therapy is needed to stabilize patients' symptoms during pregnancy or postpartum. An individualized and multidisciplinary approach involving neurologists, obstetricians, and anesthesiologists is an important consideration when monitoring these patients during pregnancy, delivery and postpartum, as this can improve the clinical outcomes in both MG mothers and their infants.

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World Journal of Obstetrics and Gynecology

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World J Obstet Gynecol 2020 December 6; 9(1): 11-17

DOI: 10.5317/wjog.v9.i1.11

ISSN 2218-6220 (online)

ORIGINAL ARTICLE

Retrospective Study

Streptococcus agalactiae: Sensitivity profile in pregnant women attending health units in northeastern Brazil

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting, critical revision and editing, and final approval of the final version.

Institutional review board statement: This research was approved by the Teaching and Research Committee of the Municipal Health Secretariat of Vitória da Conquista and approved by the Research Ethics Committee of the Universidade da Federal da Bahia, under the number CAAE 58104116.8.0000.5556 and protocol number 1.736.058.

Informed consent statement: An informed consent statement was obtained from all the individuals included.

Conflict-of-interest statement: No

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Abstract

BACKGROUND

Group B *Streptococcus agalactiae* (GBS) is the main etiologic agent associated with early-onset neonatal sepsis, and of all newborns of parturients colonized by GBS, approximately 1%-2% develop invasive, early-onset disease. The risk of infection increases to 15.2% in premature neonates, to 10.7% when the parturient has chorioamnionitis or premature rupture of membranes for more than 24 h and to 9.7% if the mother has postpartum bacteremia. In addition to causing perinatal, neonatal and postnatal deaths, neonatal hospital infection is associated with high costs, as hospitalization is three times longer than in uninfected children. The identification of pregnant women colonized by GBS, through universal screening, associated with the adoption of appropriate antibiotics at the time of delivery are the most successful preventive measures.

AIM

To evaluate the sensitivity profile of GBS isolated from pregnant women attending Vitória da Conquista-BA.

METHODS

This is a cross-sectional study with a quantitative approach carried out in the municipality of Vitória da Conquista-Bahia between February 2017 and March 2018. The study population was composed of 210 pregnant women, with a gestational age of 32 to 40 wk, who were aged 18 years or older living in the urban area of the municipality of Vitória da Conquista. After a brief explanation about the research and obtaining a signed an informed consent form, data and vaginorectal swabs were collected from the women for GBS research. Examination of the samples in order to identify the presence of GBS was by culture on sheep

potential conflicts of interest.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

Specialty type: Obstetrics and gynecology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): E

Received: April 26, 2020
Peer-review started: April 26, 2020
First decision: August 9, 2020
Revised: August 22, 2020
Accepted: September 18, 2020
Article in press: September 18, 2020
Published online: December 6, 2020

P-Reviewer: Aslam MF, Cobucci RN, Zhang XQ
S-Editor: Wang DM
L-Editor: Webster JR
P-Editor: Wang LYT

blood agar and chromogenic agar for GBS and then, seeded on plates containing streptococcal culture medium and incubated for 18 h to 24 h at 35°C. The antimicrobial sensitivity profile of positive GBS samples was determined by the disk diffusion technique, according to the Clinical and Laboratory Standards Institute manual (2017). The data obtained were stored in a database using Microsoft Office Excel spreadsheets and a descriptive analysis was performed with the aid of the EPI-INFO statistical package (version 3.5.2).

RESULTS

Among the 210 pregnant women participating in the study, 38 (18.1%) had a positive GBS culture. All strains isolated from GBS were sensitive to 10 U penicillin, 10 µg ampicillin, 30 µg cefotaxime and 30 µg vancomycin. Seven strains (18.4%) resistant to clindamycin 2 µg and eight (21.1%) resistant to erythromycin 15 µg were found. Of these, six were concomitantly resistant to erythromycin and clindamycin, two resistant only to erythromycin and one resistant only to clindamycin. All nine GBS isolates that showed resistance to erythromycin and/or clindamycin showed negative results on the D-test. Two thirds of the isolates showed cMLSB phenotype and resistance only to erythromycin in specimens in this study (02), refers to strains with phenotype M and resistance to clindamycin (01) only with phenotype L.

CONCLUSION

Chemoprophylaxis for GBS in pregnant women, especially for those allergic to penicillin, should be guided by an antimicrobial susceptibility test as resistant GBS strains were reported in this study.

Key Words: *Streptococcus agalactiae*; Sensitivity profile; Pregnancy; Clindamycin; Erythromycin; Group B streptococcal disease

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Core Tip: This is a cross-sectional study of pregnant women, with gestational age of 32-40 wk, carried out in Vitória da Conquista–Bahia. The objective was to evaluate the sensitivity profile of group B *Streptococcus agalactiae* (GBS) isolated from vaginorectal samples. 210 pregnant women participated in this investigation. Of the strains isolated, 18.4% were resistant to clindamycin and 21.1% were resistant to erythromycin. The results suggest that chemoprophylaxis for GBS should be guided by antimicrobial susceptibility testing as an important percentage of GBS strains resistant to second-choice antibiotics were observed, corroborating data in the literature from similar studies.

Citation: de Oliveira TVL, Santana FAF, Oliveira CNT, Santos MLC, de Melo FF, Souza CL, Oliveira MV. *Streptococcus agalactiae*: Sensitivity profile in pregnant women attending health units in northeastern Brazil. *World J Obstet Gynecol* 2020; 9(1): 11-17
URL: https://www.wjgnet.com/2218-6220/full/v9/i1/11.htm
DOI: https://dx.doi.org/10.5317/wjog.v9.i1.11

INTRODUCTION

Streptococcus agalactiae or group B streptococcus (GBS) is a known agent of maternal and neonatal infections. Although in most pregnant women colonization by this bacterium is generally asymptomatic, GBS may be responsible for the appearance of chorioamnionitis, endometritis, cystitis, pyelonephritis and febrile bacteremia[1,2].

Vertical transmission of this microorganism can occur in 30% to 70% of neonates whose mothers have a positive culture for this microorganism, in the absence of adequate chemoprophylaxis. In addition, one to two newborns per 1000 live births develop disease caused by this bacterium[3,4]. In this group, GBS is the main cause of sepsis and meningitis, and is a frequent cause of pneumonia[5]. The main measure to prevent neonatal GBS infection is to identify and prophylactically treat pregnant

women, thus avoiding puerperal problems and, especially, early neonatal infection[5].

In the most recent update, the Center for Disease Control and Prevention (CDC)[6] reinforces the recommendations for universal screening in the third trimester of pregnancy, through prenatal screening of GBS in material collected from the vaginal opening and the perianal region of all pregnant women who are between 35 wk and 37 wk of gestation. To prevent vertical transmission of GBS, intrapartum prophylaxis with crystalline penicillin G is recommended with 5 million units as an attack dose and 2.5 million units, every 4 h, until delivery[6].

The alternative of using erythromycin and clindamycin has increased, mainly due to patient allergy to penicillin, and as a pharmacological alternative in the absence of the antibiotic of first choice. It is important to consider the signs of increasing GBS resistance rates to these antimicrobials, according to studies carried out in different countries[7].

Resistance to macrolides, such as erythromycin, can occur by methylation of the ribosomal target site, which is the most frequent mechanism. Methylation of the RNA 23s subunit is mediated by methylases encoded by the erm (A) and erm (B) genes that confer resistance to macrolides, lincosamides, such as clindamycin, and streptogramin B, forming the MLSB phenotype, and this expression of resistance can be constitutive (cMLSB) or inducible (iMLSB)[8,9]. Alternatives to this mechanism provide resistance to only one or two of the classes of antibiotics in the MLSB8 complex.

Considering that the prevention and treatment of neonatal infection by GBS in pregnant women are not addressed in the Technical Manual for Prenatal and Puerperium-Qualified and Humanized Attention of the Ministry of Health[10], scientific research on this topic helps to substantiate the production of guidelines for adequate prophylaxis in different populations.

Thus, the objective of this work was to verify the sensitivity profile of *Streptococcus agalactiae* isolated in pregnant women attending health units in the urban area of Vitória da Conquista, Bahia State, Brazil.

MATERIALS AND METHODS

This is a cross-sectional study with a quantitative approach that was carried out in the municipality of Vitória da Conquista-Bahia between February 2017 and March 2018. The study population was composed of pregnant women, with a gestational age of 32 wk to 40 wk, attending 09 basic health units and family health units in the municipality, all located in the urban area, which were selected from the municipality's zoning and followed by drawing lots of units by area.

To calculate the sample size, an error of 5% and a 95% confidence interval were accepted, taking into account the 5191 births performed in the city in 2014 and the prevalence of colonization by GBS of 17%-referenced in a study carried out in the municipality[11]. To define the number of pregnant women in each health unit, the sample N was considered and divided proportionally into the units involved in the study. Pregnant women outside the required gestational period and under the age of 18 years who did not have authorization from those responsible for participating in the study were excluded from the study.

To collect data and samples, the pregnant women and/or guardians were approached, and, after explaining the research and signing the informed consent form, the samples were collected for GBS research. A single vaginal/rectal swab was collected from the women without a speculum by properly trained health professionals at the health units, during prenatal consultations or at scheduled times for sample collection.

The vaginorectal swabs collected from 210 pregnant women between 32 wk and 40 wk of gestation were inoculated in Stuart transport medium, placed inside boxes for biological material, at room temperature, and sent to the Clinical Analysis Laboratory of the Universidade Federal da Bahia–Campus Anísio Teixeira–Instituto Multidisciplinar em Saúde, Vitória da Conquista, Bahia State, Brazil.

The samples were placed in a chromogenic medium (Biomérieux®) for streptococci by the depletion technique, and incubated for 18 h to 24 h at 35°C to 37°C. Subsequently, the samples were placed on blood agar (Isofar®) 5% (sheep blood) and incubated for 18 h to 24 h at 35°C to 37°C in an atmosphere of 5% CO_2. Following the protocol, in order to increase the sensitivity detection, the swabs were inoculated into tubes containing Todd-Hewitt medium (Biomérieux®) at 35°C to 37°C from 18 h to 24 h. The samples were then placed in chromogenic medium (Biomérieux®) for streptococci and blood agar (Isofar®) 5% (lamb), under the same incubation conditions

as before.

For blood agar cultures suggestive of GBS (small colony growth with a grayish pattern, surrounded by a discrete halo of β-hemolysis, or without hemolysis), the catalase test, conventional Gram staining followed by microscopic analysis were performed. For Gram-positive, catalase-negative colonies, obtained from blood agar and for pink or red colonies obtained from chromogenic medium, a CAMP test (Christie, Atkins and Munch-Petersen) was performed using the kit composed of Todd-Hewitt and Hemolisinabac® (Probac do Brasil) and latex agglutination (serogroupage) using the Slidex®Strepto Plus B kit (Biomeriéux), to confirm the species.

The antimicrobial sensitivity profile of positive GBS samples was determined by the disk diffusion technique, according to the Clinical and Laboratory Standards Institute (CLSI)12 manual[12].

The evaluation of antimicrobial susceptibility was performed in Mueller Hinton medium (Isofar®) supplemented with 5% sheep blood for antibiotics: penicillin 10 U, ampicillin 10 μg, cefotaxime 30 μg, clindamycin 2 μg, erythromycin 15 μg and vancomycin 30 μg. The choice of antibiotics was made based on the technical indications of the CLSI12 manual and on the availability of medicines in the municipal health system.

To perform the D-test, bacterial suspensions were prepared in sterile saline (0.9%), with a turbidity equivalent to 0.5 on the McFarland scale obtained from recent cultures. This suspension was added to dissemination culture medium and erythromycin (15 μg) and clindamycin (2 μg) antibiotic discs were placed 12 mm apart to determine the resistance phenotype. The plates were incubated at 35-37°C and the reading was performed after 20 h to 24 h of incubation. Growth inhibition halos were measured and interpreted according to the CSLI12 manual[12].

The data were stored in a database using Microsoft Office Excel spreadsheets and a descriptive analysis was performed with the aid of the EPI-INFO statistical package (version 3.5.2).

This research was approved by the Teaching and Research Committee of the Municipal Health Secretariat of Vitória da Conquista and approved by the Research Ethics Committee of the Universidade da Federal da Bahia, under the number CAAE 58104116.8.0000.5556 and protocol number 1.736.058.

RESULTS

Of 210 pregnant women who participated in the study, 38 had a positive culture for GBS, corresponding to a prevalence of 18.1%. Table 1 presents the analysis of the sensitivity profile of GBS strains isolated from the pregnant women included in the study.

All isolated samples of GBS were sensitive to penicillin 10 U, ampicillin 10 μg, cefotaxime 30 μg and vancomycin 30 μg. Seven samples (18.4%) were resistant to clindamycin 2 μg and eight (21.1%) were resistant to erythromycin 15 μg. Of these, six were concomitantly resistant to erythromycin and clindamycin, two were resistant only to erythromycin and one resistant only to clindamycin. All nine GBS isolates that showed resistance to erythromycin and/or clindamycin showed negative results on the D-test.

DISCUSSION

The CDC6 recommendations indicate penicillin as the drug of choice for the prophylaxis of neonatal intrapartum disease. The description of GBS resistance to this antibiotic remains very low, maintaining it as the antibiotic of choice[5]. All strains of GBS isolated in this study were sensitive to penicillin. However, it is important to discuss allergy to penicillin. The literature indicates that approximately 10% of the population is allergic to B-lactams, such as penicillin[13]. For these patients, international protocols recommend the use of erythromycin and/or clindamycin, although there are reports of a significant increase in GBS resistance to these antimicrobials[7,13].

In this study, resistance to clindamycin and erythromycin was estimated at 18.4% and 21.1% respectively. These resistance rates are high when compared to the findings of Borger *et al*[7], Dutra *et al*[14] and Santos *et al*[15] in the Southeast; however, they are similar to the results found in a study carried out in the Northeast of Brazil[16].

Table 1 Susceptibility profile of group B Streptococcus samples isolated from pregnant women participating in the study (*n* = 38)

Antibiotic	Susceptible (%)	Resistant (%)
Penicillin (10 units)	100 (38/38)	-
Ampicillin (10 μg)	100 (38/38)	-
Cefotaxime (30 μg)	100 (38/38)	-
Erythromycin (15 μg)	78.9 (30/38)	21.1 (8/38)
Clindamycin (2 μg)	81.6 (31/38)	18.4 (7/38)
Vancomycin (30 μg)	100 (38/38)	-

The rates of resistance of GBS to erythromycin and clindamycin give rise to caution when using these antimicrobials for GBS prophylaxis and ratify the importance of using susceptibility tests to guide the correct choice of antimicrobials for prophylaxis in pregnant women[15].

In this study, the results of the D-test were negative for 100% of the strains of GBS isolated, indicating that there was no reduction in sensitivity induced by erythromycin or clindamycin. Two thirds of the isolates showed a cMLSB phenotype, in agreement with the results of Martínez *et al*[17]. Resistance only to erythromycin in specimens in this study (02), refers to strains with phenotype M and resistance to clindamycin (01) only with phenotype L[18,19].

In these same GBS strains analyzed in the present investigation, resistance genes - mefA gene and genes of the *erm* family[20]- were identified in another study developed in parallel, corroborating the findings described here. These genes confer resistance to macrolides and the MSLB complex, respectively[19]. However, according to Santana[20], resistance to clindamycin could be associated with other resistance genes that were not tested in the study in question.

All strains were sensitive to ampicillin, cefotaxime and vancomycin, corroborating findings in the national literature by Borger *et al*[7], Dutra *et al*[14], Santos *et al*[15]. In the present study, GBS sensitivity to ceftriaxone was not evaluated; however, it is important to note that Andrade *et al*[16] found resistance of 12.7% to this antibiotic.

CONCLUSION

The results of this work reinforce the importance of knowing the sensitivity profile for GBS. The observed rates of resistance to erythromycin and clindamycin indicate the need for more adequate and responsible management, especially in patients with a history of allergy to penicillin or when this drug is not available. Adequate management is very relevant in the clinical context as it prevents the evolution of possible complications in neonates and thus contributes greatly to reducing morbidity and mortality. It also effectively reduces costs due to hospitalizations and more complex procedures, and decreases the occupancy of beds in neonatal ICUs, optimizing their use for non-preventable causes.

ARTICLE HIGHLIGHTS

Research background

Streptococcus agalactiae (Group B *Streptococcus*, GBS) is a bacterium known to be a causative agent of maternal and neonatal infections. The colonization of pregnant women by GBS, although most patients are asymptomatic, represents a risk for several pathologies, from chorioamnionitis, endometritis, cystitis, and pyelonephritis to febrile bacteremia. In addition, this infection can trigger pneumonia, meningitis and sepsis in neonates. To prevent this vertical transmission, prophylaxis with crystalline penicillin G or macrolides is recommended. However, with increasing levels of resistance, it is necessary to know the local resistance profile regarding adequate antimicrobial use.

Research motivation

It is important to identify and prophylactically treat pregnant women to avoid

puerperal problems, especially early neonatal infection. In this sense, knowledge on GBS colonization detection and resistance rates to standard treatments is essential for clinical practice on GBS disease.

Research objectives

To verify the sensitivity profile of *Streptococcus agalactiae* isolated in pregnant women attending health units in the urban area of Vitória da Conquista, in Bahia State, Brazil.

Research methods

This is a cross-sectional study with a quantitative approach where 210 vaginorectal swabs collected from pregnant women attending health units in the county of Vitória da Conquista, in Bahia State, Brazil were analyzed. Pregnant women with gestational ages from 32 wk to 40 wk were eligible for this study. A single vaginal/rectal swab was collected from the women without a speculum, inoculated into Stuart transport medium, and placed in a chromogenic medium (Biomérieux®) for streptococci by the depletion technique. Subsequently, the samples were added to blood agar (Isofar®) 5% (sheep blood) incubated for 18 h to 24 h at 35°C to 37°C in an atmosphere of 5% CO_2. The swabs were then inoculated into tubes containing Todd-Hewitt medium (Biomérieux®) at 35°C to 37°C from 18 h to 24h and then into chromogenic medium (Biomérieux®) for streptococci and blood agar (Isofar®) 5% (lamb).

All small colony growth with a grayish pattern, surrounded by a discrete halo of β-hemolysis, or without hemolysis (characteristics for GBS identification) underwent the catalase test and conventional Gram staining followed by microscopic analysis. For Gram-positive, catalase-negative colonies, obtained from blood agar and pink or red colonies obtained from chromogenic medium, a CAMP test (Christie, Atkins and Munch-Petersen) was performed using the kit composed of Todd-Hewitt and Hemolisinabac® (Probac do Brasil) and latex agglutination (serogroupage) using the Slidex®Strepto Plus B kit (Biomeriéux), to confirm the species. The antimicrobial sensitivity profile of positive GBS samples was determined by the disk diffusion technique, according to the CLSI12 manual, in Mueller Hinton medium (Isofar®) supplemented with 5% sheep blood.

Research results

Among the 210 pregnant women participating in the study, 38 (18.1%) had a positive GBS culture. All GBS strains isolated were sensitive to 10 U penicillin, 10 μg ampicillin, 30 μg cefotaxime and 30 μg vancomycin. Seven strains (18.4%) resistant to clindamycin 2 μg and eight (21.1%) resistant to erythromycin 15 μg were observed. Of these, six were concomitantly resistant to erythromycin and clindamycin, two resistant only to erythromycin and one resistant only to clindamycin. All nine GBS isolates that showed resistance to erythromycin and/or clindamycin showed negative results on the D-test. Two thirds of the isolates showed cMLSB phenotype and resistance only to erythromycin in specimens in this study (02), refers to strains with phenotype M and resistance to clindamycin (01) only with phenotype L.

Research conclusions

Chemoprophylaxis for GBS in pregnant women, especially for those allergic to penicillin, should be guided by an antimicrobial susceptibility test as resistant GBS strains were reported in this study.

Research perspectives

The information provided by this study is applicable for the elaboration of GBS guidelines for adequate prophylaxis in different populations.

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