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Severe Maternal Morbidity due to infection and H1N1 influenza in the Brazilian Network for the Surveillance of Severe Maternal Morbidity

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Tocoginecologia, da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para a obtenção do título de Mestre em Ciências da Saúde, área de concentração em Saúde Materna e Perinatal.

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ORIENTADOR: Profª. Dra. MARIA LAURA COSTA DO NASCIMENTO

CO-ORIENTADOR: Prof. Dr. JOSÉ GUILHERME CECATTI

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Resumo

Introdução: A infecção representa importante causa de morbidade e mortalidade materna no mundo. Doenças respiratórias graves (DRG), especialmente as virais, se destacam pelo seu potencial de epidemia com maior vulnerabilidade na gestação. **Objetivo:** Avaliar o impacto da morbidade materna grave (MMG) atribuível à infecção grave (em especial sepse e influenza A(H1N1)pdm09) e os fatores associados ao pior resultado materno (near miss e óbito), entre mulheres da Rede Brasileira de Vigilância da Morbidade Materna Grave. **Métodos:** estudo transversal multicêntrico com vigilância prospectiva de mulheres com MMG em 2009/2010, utilizando os critérios da Organização Mundial da Saúde de condições potencialmente ameaçadoras da vida (CPAV) e near miss materno (NMM). Para avaliação dos casos de infecção foram selecionadas as variáveis: sepse grave, suspeita ou confirmação de H1N1 e meningite; enquanto insuficiência respiratória aguda e suspeita ou confirmação de H1N1 foram variáveis avaliadas para os casos de doença respiratória grave (DRG). Casos com suspeita de A(H1N1)pdm09 foram revisados e subdivididos: não-testados, confirmados e não confirmados para A(H1N1)pdm09 e os seus resultados comparados entre si e com outras causas de MMG, com os respectivos indicadores de saúde. Os principais focos de infecção também foram avaliados conforme resultado materno. Fatores associados com NMM e MM foram analisados para os dois grupos usando Razão de Prevalência e Intervalo de confiança de 95% ajustados para o efeito cluster do desenho do estudo. Valores estatisticamente significativos foram considerados para $p<0,05$. A regressão múltipla de Poisson identificou fatores independentemente

associados a maior gravidade para os casos de infecção. **Resultados:** 82.388 mulheres vigiadas, 9555 casos de MMG e 502 (5,3%) casos de infecção grave. Infecção grave foi responsável por aproximadamente um quarto dos casos de NMM e quase metade dos casos de MM, sendo o principal foco de infecção o pulmonar (impacto da pandemia A(H1N1)pdm09), seguido pelo uterino. O terceiro foco mais prevalente foi o urinário, associado a maior severidade. Os indicadores de saúde demonstraram maior gravidade dos casos complicados por infecção e DRG. Para DRG, 206 mulheres apresentaram suspeita de A(H1N1)pdm09, cerca de 60% foram testadas para a doença e 49 mulheres confirmaram diagnóstico. Casos de A(H1N1)pdm09 positivo apresentaram piores desfechos e taxa de NMM:MM abaixo de 1 (0,9:1), (12:1 outras causas de MMG). Demoras no atendimento ocorreram em mais de 50% dos casos de infecção, associadas a pior prognóstico materno e elevaram em duas vezes o risco de desfecho materno grave para DRG. Resultados perinatais foram piores dentre os casos de DRG, com aumento da prematuridade, morte fetal, baixo peso ao nascer e Apgar <7. HIV/AIDS, histerectomia, hospitalização prolongada, admissão em UTI e demoras no atendimento foram alguns fatores independentes associados a pior desfecho. **Conclusão**: infecção grave, especialmente por influenza A(H1N1)pdm09 geram grande impacto sobre morbidade e mortalidade materna no Brasil. Compreender os fatores associados à maior gravidade pode colaborar para a melhoria do cuidado obstétrico. Investir em intervenções específicas para gravidez, visando diagnóstico precoce e tratamento oportuno são essenciais para melhorar a saúde materna e reduzir o número de mortes maternas evitáveis no país.

Palavras-chave: Infecção; Sepse; Influenza A Virus H1N1 subtipo; Morbidade materna grave; Near Miss; Mortalidade materna.

Abstract

Background: Infection represents a major cause of maternal morbidity and mortality with growing concern worldwide. Respiratory diseases, especially viral, have stood out because of their epidemic potential and the identified vulnerability during pregnancy. **Objective:** To assess the impact of severe maternal morbidity (SMM) due to severe infection (especially sepsis and H1N1 influenza) and factors associated with worse maternal outcome (near miss and death) among women of the Brazilian Network for the Surveillance of Severe Maternal Morbidity. **Methods:** cross-sectional, multicenter study of 27 obstetric referral centers in five brazilian regions in 2009/2010. Prospective surveillance of severe infection was performed using the World Health Organization (WHO) criteria of potentially life threatening conditions (PLTC) and maternal near miss (MNM). Complications due to infection were identified upon the variables available as severe sepsis, suspected or confirmed H1N1 influenza or meningitis (which contributed with 2 cases) and compared to other causes of SMM. Respiratory diseases were assessed as respiratory insufficiency and suspected or confirmed H1N1. Cases of suspected A(H1N1)pdm09 were reviewed and divided into: non-tested, confirmed and unconfirmed for A(H1N1)pdm09 and their results were compared among these groups and to cases of other causes of morbidity.. Factors associated with SMO were assessed in both groups, using PR and 95%CI adjusted for design effect of cluster sampling and values were considered significant if $p<0.05$. **Results:** Among the 9555 cases of SMM, only 502 (5.3%) had severe infection, however they were responsible for about a quarter of cases of MNM and almost half of the cases of maternal mortality (MM). The assessed health indicators

demonstrate greater severity of cases complicated by infection, with a mortality index (MI) above 26% compared to 11% for other causes of SMM. The most prevalent site of infection was pulmonary (due to the pandemic influenza season), followed by uterine and urinary, which was most related to increased severity. For respiratory disease, 206 women had suspected A(H1N1)pdm09, about 60% were tested for the disease and 49 women were positive. The severity of the maternal outcomes was worse between the cases of A(H1N1)pdm09 positive, with a rate of MNM: MM below 1 (0.9: 1), compared to 12: 1 for other SMM causes. The MI among respiratory disease was superior to 50% (7.4% other causes SMM). Delays in care were associated with worse maternal prognosis and were present in over 50% of cases of infection. Perinatal results were worse in cases of respiratory disease, with increased prematurity, stillbirth, low birth weight and Apgar <7. HIV/AIDS, hysterectomy, prolonged hospitalization, ICU admission and delays in care were independent factors associated with severe maternal outcome. **Conclusion:** severe infections and especially those caused by A(H1N1)pdm09 presented great impact on maternal morbidity and mortality in Brazil and the identification of factors associated with the increased severity can contribute to the improvement of obstetric care. There is need for specific interventions during pregnancy, seeking early diagnosis and timely treatment of infections, which are essential for improving maternal health and to reducing the number of preventable maternal deaths in the country.

Keywords: infection; sepsis; Influenza A Viurs H1N1 subtype; severe maternal morbidity; near miss; maternal mortality.

Sumário

Dedicatória

Dedico este trabalho...

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mediram esforços para que eu estudasse mesmo longe de casa.

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Siglas e Abreviaturas

AIDS – *Acquired Immunodeficiency Syndrome*

ARDS – *Acute Respiratory Distress Syndrome*

CEP – Comitê de Ética em Pesquisa

CI – *Confidence Interval*

CID-10 – Classificação Internacional de Doenças 10ª edição

CNPq – Conselho Nacional de Desenvolvimento Cintífico e Tecnológico

CONEP – Conselho Nacional de Ética em Pesquisa

CPAV – Condições Potencialmente Ameaçadoras da Vida

CRP – *Cardiopulmonary Resuscitation*

DECIT – Departamento de Ciência e Tecnologia do Ministério da Saúde do Brasil

HELLP – *Hemolysis, Elevated Liver enzimes, Low Plaquetscount*

HIV – *Human Immunodeficiency Virus*

ICU – *Intensive Care Unit*

IM – Índice de Mortalidade

LB – *Live Births*

MD – *Maternal death*

MI – *Mortality Index*

MM – Morte Materna

MMR – *Maternal Mortality Ratio*

MNM – *Maternal Near Miss*

MNMR – *Maternal Near Miss Ratio*

NICU – *Neonatal Intensive Care Unit*

NMM – Near Miss Materno

OMS – Organização Mundial da Saúde

PASS – *Pregnancy-associated Severe Sepsis*

PLTC – *Potentially Life Threatening Conditions*

PR – *Prevalence Ratio*

RBVMMG – Rede Brasileira de Vigilância de Morbidade Materna Grave

RR – *Respiratory Rate*

SIRS – *Systemic Inflammatory Response Syndrome*

SMM – *Severe Maternal Morbidity*

SMO – *Severe Maternal Outcome*

SMOR – *Severe Maternal Outcome Ratio*

UNICAMP – Universidade Estadual de Campinas

USA – *United States of America*

USPRP – Universidade de São Paulo em Ribeirão Preto

WHO – *World Health Organization*

1. Introdução

1.1. Mortalidade Materna

Segundo a 10ª Revisão da Classificação Internacional de Doenças (CID-10), morte materna é a "morte de uma mulher durante a gestação ou até 42 dias após o término da gestação, independente da duração ou da localização da gravidez, devida a qualquer causa relacionada com ou agravada pela gradidez ou por medidas em relação a ela, porém não devida a causas acidentais ou incidentais" (1). Quando esta morte é resultante de complicações obstétricas ocorridas na gravidez, parto ou puerpério, é classificada como morte obstétrica direta (pré-eclâmpsia, eclâmpsia, aborto, hemorragia, infecção de foco uterino) e, quando é resultante de doenças pré-gestacionais ou que se desenvolveram durante a gestação, não devido a causas obstétricas diretas, mas que foram agravadas pelos efeitos fisiológicos da gravidez, é classificada como morte obstétrica indireta (como: infecção de foco não uterino, hipertensão pré-existente à gestação, cardiopatia) (1).

A melhoria da saúde materna tem sido foco de atenção mundial desde sua definição como 5º objetivo de desenvolvimento do milênio. Entretanto, o acordo internacional para reduzir a mortalidade materna em ¾ entre 1990 e 2015 (2) ainda hoje é um desafio para diversos países.

Estimou-se que no ano de 2013 cerca de 289.000 mortes maternas tenham ocorrido no planeta; destas quase 99% ocorreram nos países de baixa e média renda (3). As disparidades econômicas e sociais existentes no mundo são claramente expressas nas taxas de mortalidade materna que chegam a ser mais de 100 vezes menor nos países de alta renda quando comparados a países com menos recursos (3,4).

Hemorragia grave, distúrbios hipertensivos da gravidez, infecções, complicações no parto e abortamento inseguro são as principais causas de morte materna e representam cerca de 75% do total de óbitos maternos no mundo (5). Contudo, nos últimos anos, é possível observar, globalmente, uma mudança em relação ao padrão das taxas de mortalidade com aumento da prevalência de causas indiretas, institucionalização e medicalização do parto, bem como do número de intervenções obstétricas – fenômeno que foi denominado “transição obstétrica” (6).

No Brasil, as causas obstétricas diretas são responsáveis por mais da metade dos óbitos maternos, sendo cerca de 5,6% por complicações hipertensivas, 0,6% por complicações hemorrágicas, 0,2% por complicações infecciosas (7), entretanto é possível observar um aumento das causas indiretas no país nos últimos anos (8). Embora seja notável o progresso na área materno-infantil, muito como consequência de melhorias sociais e econômicas no período, a meta de redução da taxa de mortalidade materna não será alcançada neste ano (6,8).

1.2. Morbidade Materna Grave

Levando-se em consideração que para cada morte materna, um número maior de mulheres sobrevive às complicações graves durante a gestação, parto e puerpério, a vigilância dos casos de morbidade materna grave ganhou destaque na última década, justamente por permitir uma melhor investigação de cada caso, visto que a mulher ainda está viva (9,10). Dentro deste contexto, a padronização pela Organização Mundial da Saúde (OMS) dos conceitos de

"condições potencialmente ameaçadoras da vida" (CPAV) e "near miss materno" (NMM) contribuiu de maneira significativa não somente para a compreensão dos casos de morbidade materna, mas também para a adequada comparação de estudos em diversos cenários (11).

Condições potencialmente ameaçadoras da vida ocorrem na presença de complicações maternas, incluindo distúrbios hemorrágicos e hipertensivos, além de indicadores de manejo de gravidade e outras complicações (Fig. 1). Já NMM foi definido como "uma mulher que quase morreu, mas que sobreviveu a uma complicação grave durante o período gestacional até 42 dias após o término da gestação", com pelo menos um dos critérios clínicos, laboratoriais ou de manejo (Fig. 2) (11).

COMPLICAÇÕES HEMORRÁGICAS	
Descolamento prematuro de placenta Placenta Prévia / acreta / increta / percreta Gravidez Ectópica Rotura uterina Hemorragia grave por aborto	Hemorragia pós-parto a) Atonia b) Retenção placentária c) Lacerações de Trajeto d) Coagulopatia
COMPLICAÇÕES HIPERTENSIVAS	
Pré-eclâmpsia grave Eclâmpsia	Hipertensão grave HELLP Síndrome
OUTRAS COMPLICAÇÕES	
Edema pulmonar Conculsões Sepse grave a) Endometrite pós-parto b) Endometrite pós-aborto c) Foco urinário d) Foco pulmonar Trombocitopenia < 100mil Crise Tireotóxica Choque	Insuficiência Respiratória Aguda Acidose Cardiopatia Acidente Vascular Cerebral Distúrbio de coagulação Tramboembolismo Cetoacidose Diabética Icterícia / Disfunção Hepática Meningite Insuficiência Renal Aguda
INDICADORES DE MANEJO DE GRAVIDADE	
Transfusão de hemoderivados Acesso venoso central Admissão em UTI Hospitalização Prolongada (>7dias)	Intubação não relacionada à anestesia Retorno à sala cirúrgica Intervenção cirúrica maior (histerectomia, laparotomia) Uso de Sulfato de Magnésio

Figura 1. Condições Potencialmente Ameaçadoras da Vida (Say et al., 2009)

CRITÉRIOS CLÍNICOS	
Cianose aguda *Gasping* Frequência respiratória >40 ou <6 irpm Choque Oligúria não resposiva a fluidos ou diuréticos Distúrbio de coagulação	Perda de consciência durante 12h ou mais Ausência de consciência e pulso/batimento cardíaco Acidente vascular cerebral Convulsão não controlada / paralisia total Icterícia na presença de pré-eclâmpsia
CRITÉRIOS LABORATORIAIS	
Saturação de Oxigênio <90% por mais de 60min PaO2/FiO2 <200 Creatinina $\geq$ 300mmol/l ou $\geq$3,5 mg/dl Bilirrubina $\geq$ 100 mmol/l ou $\geq$ 6,0 mg/dl	pH <7,1 Lactato > 5 Trombocitopenia aguda (<50.000 plaquetas) Ausência de consciência e presença de glicose e cetoacidose na urina
CRITÉRIOS DE MANEJO	
Uso de droga vasoativa contínua Histerectomia puerperal por infecção ou hemorragia Transfusão de $\geq$5 unidades de concentrado de hemácias	Intubação e ventilação por tempo $\geq$60 min, não relacionada com anestesia Diálise para insuficiência renal aguda Reanimação cardio-pulmonar (RCP)

Figura 2. Critérios de Near Miss Materno (Say et al., 2009)

A partir destes conceitos de CPAV e NMM, a OMS desenvolveu um conjunto de indicadores de saúde que contribuiu para a avaliação da qualidade do atendimento obstétrico dentro dos hospitais/maternidades (11). A padronização destes indicadores de saúde (Fig. 3) é fundamental para a compreensão da morbidade materna e adequada comparação entre as diversas instituições de cuidado obstétrico.

Razão de desfecho materno grave (RDMG) refere-se ao número de mulheres com condições ameaçadoras à vida por 1.000 nascidos vivos (NV). Este indicador fornece uma estimativa da quantidade de cuidado e recursos que seriam necessários em uma instituição de saúde [RDMG = (NMM +MM)/NV].

Razão de Near Miss Materno (RNM) refere-se ao número de casos de near miss materno por 1.000 nascidos vivos (RNM = NMM/NV). De forma similar ao RDMG, este indicador apresenta uma estimativa sobre o volume de cuidado e recursos que seriam necessários em uma instituição de saúde.

Razão entre near miss materno e mortalidade (NMM: 1 MM) refere-se à razão entre casos de near miss e óbitos maternos. Razões mais altas indicam um atendimento melhor.

Índice de Mortalidade (IM) refere-se ao número de óbitos maternos dividido pelo número de mulheres com condições ameaçadoras à vida, expresso como um percentual [IM = MM/(NMM + MM)]. Quanto mais alto for o índice, mais mulheres com condições ameaçadoras à vida morrem (baixa qualidade de atendimento), e quanto menor for o índice, menos mulheres com condições ameaçadoras à vida morrem (melhor qualidade de atendimento).

Figura 3: Indicadores de Saúde (WHO, 2011)

1.3. Infecção grave

Complicações de causa infecciosa geram significativa morbidade e mortalidade durante a gestação, parto e puerpério, sendo uma preocupação crescente no mundo todo, tanto entre países de média e baixa renda, como também nos países de alta renda (12). Mesmo que ainda seja um evento raro quando comparado à alta ocorrência de outras causas de morbidade materna como os distúbios hipertensivos e hemorrágicos, as infecções graves na gestação têm grande impacto sobre a mortalidade.

A gravidez é um momento de difícil diagnóstico da doença infecciosa devido às alterações fisiológicas que modulam o período e à susceptibilidade do organismo materno à infecção. Adaptações do organismo materno durante a gravidez, como taquicardia, taquipnéia, hipotensão e aumento da contagem de glóbulos brancos podem dificultar o diagnóstico de infecção, elevando a gravidade do caso devido ao manejo tardio desta complicação (12-16).

Sabidamente, durante a gestação ocorrem intensas modificações no sistema cardiovascular, função pulmonar, função renal, aparelho gastrointestinal e coagulação e todas elas podem, na vigência de infecção grave, favorecer a progressão da doença (17). Além disso, condições pré-existentes, como anemia ou a presença de comorbidades, por exemplo

obesidade ou infecções crônicas, como o HIV, podem influenciar a resposta ou evolução de uma complicação infecciosa aguda (18).

O estudo da resposta imune durante a gestação seja para a definição de mecanismos de tolerância que expliquem a interação materno-fetal, ou para a compreensão de suscetibilidade a infecção e resposta inflamatória durante a gravidez tem expandido muito na última década, mas ainda existem muitas dúvidas quanto ao papel dos diferentes tipos celulares e dos "gatilhos" necessários para ativação imune (14,19).

1.3.1. Sepse na gestação

A sepse ou septicemia é definida pelo CID-10 como uma síndrome de resposta inflamatória sistêmica de etiologia infecciosa suspeita ou comprovada (1). Já a sepse grave, representa o caso de sepse complicado por disfunção orgânica ou hipoperfusão tecidual (20).

As mortes maternas relacionadas à sepse frequentemente estão associadas com incapacidade de reconhecer a gravidade da doença (12). Sabe-se que a identificação precoce e tratamento adequado são fundamentais para a redução das taxas de óbito por causas infecciosas. Neste sentido, campanhas internacionais sobre sepse, sepse grave e choque séptico vêm sendo publicadas constantemente no mundo todo (21).

Entretanto, as diretrizes internacionais não abordam as especificidades do período gestacional e puerperal (12). Essa falta de critério específico para a definição de sepse durante a gestação é também observada nas publicações recentes sobre o assunto, onde a maioria das avaliações são retrospectivas, com tamanho de amostra restrito e definições pouco claras em relação à sepse materna e à fase gestacional (18).

Mundialmente, observa-se que, apesar dos avanços na assistência à mulher, a taxa de mortalidade relacionada à sepse materna ainda é alta, sendo estimado que ocorram anualmente 62.000 mortes maternas por ano no mundo todo por esta causa (12). Em países de alta renda como os EUA, embora o risco absoluto de morte materna por sepse seja relativamente baixo (0,60 por

100.000 nascidos vivos), o risco de morbidade é substancialmente maior (20,9 por 100.000 partos) (15). Em países de média-baixa renda, a taxa de mortalidade por sepse chega a ser responsável por até 11,6% de todas as mortes maternas (12). Entretanto, pouco se conhece sobre a epidemiologia da sepse durante a gestação, parto e puerpério no Brasil.

1.3.2. Doença Respiratória e A(H1N1)pdm09

Dentro das causas indiretas de morte materna, nos últimos anos as doenças virais e infecciosas do trato respiratório têm se destacado justamente pelo potencial de epidemia com que ameaçam a saúde da população mundial (22) e pelo reconhecido risco elevado de complicações graves associadas à influenza (23,24). No entanto, a falta de uniformidade existente na apresentação de trabalhos sobre as complicações respiratórias dificulta a interpretação dos dados (25).

Com origem no México no final de março de 2009, a pandemia causada pelo vírus A(H1N1)pdm09 atingiu diversos países e comunidades (26) e foi a infecção viral com maior morbidade e mortalidade em gestantes e puérperas registrada no mundo nas últimas décadas (26,27).

Durante a pandemia pelo vírus A(H1N1)pdm09 gestantes apresentaram sintomatologia de amplo estrectro, variando de quadros não-febris a infecção leve de via aérea superior ou pneumonia grave ou fatal (28). Dentre os sintomas mais comuns, destacam-se a febre de início súbito (normalmente maior do que 38ºC), tosse, dor de garganta, mal-estar, dor muscular e nas articulações e dor de cabeça (28).

Segundo a OMS, mulheres grávidas, especialmente as com comorbidades, além de serem mais propensas a desenvolver complicações graves de todas as formas de infecção pelo vírus influenza, apresentam risco aumentado para efeitos adversos da gravidez como abortamento espontâneo, parto prematuro e sofrimento fetal (28). Tendo em vista a rapidez com que a doença evolui para piores desfechos, o tratamento com antiviral continua sendo indicado para todas as gestantes, assim como a vacinação (23).

1.4. Rede Brasileira de Vigilância de Morbidade Materna Grave

Frente à relevância do estudo da morbidade materna, em 2009 foi criada a Rede Brasileira de Vigilância de Morbidade Materna Grave (RBVMMG) para avaliação dos determinantes de mortalidade materna através dos recentes critérios de near miss materno e condições potencialmente ameaçadoras da vida em gestantes e puérperas nas cinco regiões do Brasil. Caracterizado como um estudo multicêntrico e de corte transversal, a RBVMMG contou com a participação de 27 centros de referência obstétrica do Brasil no período de julho de 2009 a junho de 2010.

Os resultados desta avaliação culminaram na vigilância de 82388 mulheres, 9555 casos de morbidade materna, sendo 8645 casos de condição potencialmente ameaçadora da vida, 770 casos de near miss e 140 de morte materna. Vários estudos já foram publicados até o momento com análises em relação aos distúrbios hemorrágicos e hipertensivos, pré-eclâmpsia e demoras no atendimento obstétrico, entre outros (29-36), sendo a avaliação da morbidade por causa infecciosa também prevista entre as análises propostas inicialmente para este estudo.

Dessa forma, este estudo objetivou avaliar a ocorrência de complicações maternas graves atribuíveis à infecção em comparação com as demais causas de morbidade grave e os fatores associados à evolução para pior prognóstico entre os casos de infecção na Rede Brasileira de Vigilância de Morbidade Materna Grave. A definição dos casos foi proposta segundo as variáveis disponíveis na ficha de coleta de dados (Anexo 2) relacionadas à infecção: sepse grave, suspeita ou confirmação de H1N1 e meningite e à doença respiratória grave: suspeita ou confirmação de H1N1 e insuficiência respiratória aguda.

1.4.1 Definição das principais variáveis para este estudo

Complicação associada à suspeita ou confirmação de Influenza A (H1N1): condição de gravidade decorrente ou associada à infecção suspeita ou confirmada do vírus Influenza H1N1. Casos leves, de evolução favorável e sem

indicadores de clínicos, laboratoriais ou de manejo de gravidade não devem ser incluídos no estudo. Casos com confirmação laboratorial do vírus após a inclusão no estudo deverão ter esta informação editada no formulário.

Sepse grave: pelo menos um dos sinais da síndrome de resposta inflamatória sistêmica (SIRS) associado à infecção documentada ou suspeita e pelo menos 1 dos sinais de disfunção orgânica aguda secundária à infecção.

- SIRS: febre (> 38,3°C) ou hipotermia (<36°C); taquicardia (FC>90bpm); taquipnéia (FR>20 irpm ou PaCO2 <32mHg); leucocitose (≥12000/mm³) ou leucopenia (≤4000/mm³) ou >10% de bastões.
- Disfunção orgânica: alteração do nível de consciência, hiperglicemia na ausência de diabetes (> 140 mg/dl), hipotensão (PA sistólica < 90mmHg ou PA média < 70 mmHg), hipoxemia (PaO2/FiO2 < 300), oligúria (diurese < 0,5 ml/kg por pelo menos 2 horas, apesar de reposição adequada de fluidos), aumento de creatinina > 0,5 mg/dl ou creatinina > 2 mg/dl, coagulopatia (RNI > 1,5), íleo, plaquetopenia < 100.000, hiperbilirrubinemia (bilirrubina total > 2 mg/dl), hiperlactatemia (acima do valor de referência).

Insuficiência respiratória aguda: incapacidade do sistema respiratório em promover adequada troca gasosa, com parâmetros gasométricos de: PaO2 < 60 mmHg ou Saturação periférica < 90%, associado ou não à PaCO2 > 50 mmHg. Parâmetros clínicos podem ser observados, como: taquipnéia (FR > 20) ou bradipnéia (FR<6), uso de musculatura acessória, batimento de asa de nariz, associados a torpor ou agitação, entre outros.

2. Objetivos

2.1. Objetivo Geral

Avaliar o impacto da morbidade materna grave atribuível à infecção e os fatores associados ao pior resultado materno (near miss e óbito), entre mulheres da Rede Brasileira de Vigilância de Morbidade Materna Grave.

2.2. Objetivos Específicos

- Avaliar a frequência, indicadores de saúde, as características sócio-demográficas, clínicas e obstétricas de mulheres com morbidade materna grave por infecção (sepse, meningite e suspeita ou confirmação de A(H1N1)pdm09), comparadas a mulheres com outras causas de morbidade (como hipertensão e hemorragia) e os fatores associados à evolução para maior gravidade (near miss e óbito materno) para os casos de infecção.

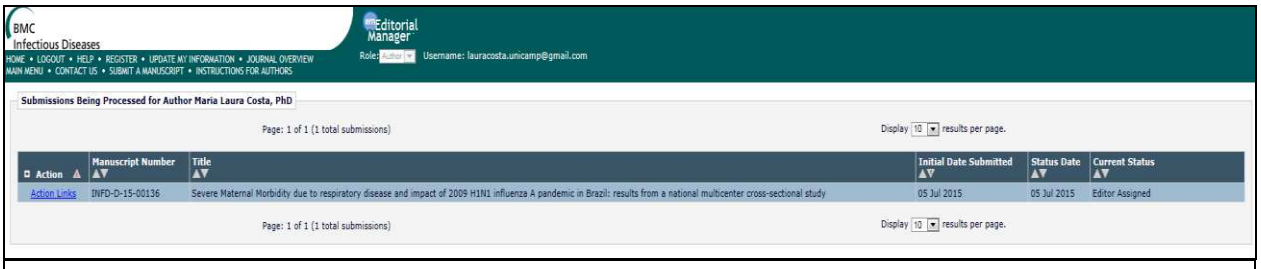
- Avaliar a frequência, indicadores de saúde, as características sócio-demográficas, clínicas e obstétricas de mulheres com morbidade

materna grave por doença respiratória (insuficiência respiratória aguda e suspeita ou confirmação de A(H1N1)pdm09), comparadas a mulheres com outras causas de morbidade grave (como hipertensão e hemorragia) e os fatores associados à evolução para maior gravidade (near miss e óbito materno) nos dois grupos.

3. Publicações

3.1. Artigo 1

Pfitscher LC, Cecatti JG, Pacagnella RC, Haddad SM, Parpinelli MA, Souza JP, Quintana SM, Surita FG, Sousa MH, Costa ML, for the Brazilian Network for Surveillance of Severe Maternal Morbidity study group. Severe Maternal Morbidity due to respiratory disease and impact of 2009 H1N1 influenza A pandemic in Brazil: results from a national multicenter cross-sectional study. BMC Infectious Diseases 2015 (Submitted).



BMC Infectious Diseases

Severe Maternal Morbidity due to respiratory disease and impact of 2009 H1N1 influenza A pandemic in Brazil: results from a national multicenter cross-sectional study

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RESEARCH ARTICLE

Severe Maternal Morbidity due to respiratory disease and impact of 2009 H1N1 influenza A pandemic in Brazil: results from a national multicenter cross-sectional study

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Running title: Severe Maternal Morbidity and respiratory disease

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Abstract

Background: The aim of this study was to assess the burden of respiratory disease, considering the influenza A pandemic season (H1N1pdm09), within the Brazilian Network for Surveillance of Severe Maternal Morbidity, and factors associated with worse maternal outcome.

Methods: A multicenter cross-sectional study, involving 27 referral maternity hospitals in five Brazilian regions. Cases were identified in a prospective surveillance by using the WHO standardized criteria for potentially life-threatening conditions (PLTC) and maternal near miss (MNM). Women with severe complications from respiratory disease identified as suspected or confirmed cases of A(H1N1)pdm09 influenza or respiratory failure were compared to those with other causes of severe morbidity. A review of suspected A(H1N1)pdm09 influenza cases classified women as non-tested, tested positive and tested negative, comparing their outcomes. Factors associated with severe maternal outcome (SMO) were assessed in both groups, using PR and 95%CI adjusted for design effect of cluster sampling.

Results: Among 9555 cases of severe maternal morbidity, 485(5%) had respiratory disease. Respiratory disease occurred in one-quarter of MNM cases and two-thirds of maternal death (MD). A(H1N1)pdm09 virus was suspected in 206 cases with respiratory illness. Around 60% of these women were tested, yielding 49 confirmed cases. Confirmed A(H1N1)pdm09 influenza cases had worse adverse outcomes (MNM:MD ratio < 1 (0.9:1), compared to 12:1 in cases due to other causes), and a mortality index > 50%, in comparison to 7.4% in other causes of severe maternal morbidity. Delay in medical care was associated with worse maternal outcome and a two-fold increased risk of SMO in respiratory disease patients. Perinatal outcome was worse in cases complicated by respiratory disease, with increased prematurity, stillbirth, low birth weight and Apgar score <7.

Conclusions: Respiratory disease, especially considering the influenza season, is a very severe cause of maternal near miss and death. Increased awareness of this condition, preventive vaccination during pregnancy, early diagnosis and treatment are required to improve maternal health.

Keywords: *maternal morbidity; maternal mortality; maternal near miss; respiratory dise*ase*; influenza A Virus H1N1 subtype.*

Background

Improvement in maternal health and a reduction in maternal mortality have received priority worldwide, in an attempt to accomplish the established millennium development goals set for 2015 [1-3]. However, the expected reduction in maternal mortality is still far from ideal and varies widely across regions [4,5]. Most recently, to better comprehend the burden of disease on female health and complement mortality inquiries, an alternative approach has been to study maternal morbidity. Maternal morbidity can have an impact on both low-income and high-income settings.

In 2009, the World Health Organization (WHO) standardized the definitions of potentially life-threatening conditions (PLTC) and maternal near miss (MNM) [6]. PLTC is defined by the number of maternal complications, including hemorrhagic (e.g. abruption placenta, ruptured uterus, atony and others), hypertensive disorders (e.g. severe preeclampsia, eclampsia, HELLP syndrome), management indicators of severity (e.g. blood transfusion, intubation, intensive care unit admission) and other complications (e.g. pulmonary edema, cardiac disease and sepsis). Maternal near miss is any situation in which a woman survives a very severe complication with proven organ dysfunction, during pregnancy or puerperium (42 days after childbirth), with at least one of the following criteria: clinical (e.g. shock or clotting disorder), laboratory (lactate>5, $PaO_2/FiO_2 < 200$ mmHg) or management (hysterectomy due to infection or hemorrhage and blood transfusion ≥ 5 units of packed red blood cells) [6].

Recently, the concept of “obstetric transition” was incorporated into the study of maternal morbidity and mortality. The concept illustrates a global trend in which a pattern of high maternal mortality rates with predominantly direct obstetric causes (e.g, hemorrhage, preeclampsia or uterine infection) has been replaced by lower maternal mortality rates with an increasing proportion of indirect causes (preexisting disorders or those aggravated by pregnancy, such as cardiac disease, kidney disease or infection due to urinary or pulmonary foci), institutionalization and medicalization of childbirth and increased rate of obstetric interventions [7]. Obstetric transition is important to help understand the occurrence of severe maternal morbidity and provide patients with the appropriate treatment in different settings.

Among the indirect causes of maternal morbidity and mortality, respiratory disease plays a significant role, either due to the presence of severe infection or complications of the underlying conditions, such as asthma and heart disease. Physiological and anatomical changes that occur during pregnancy to provide accommodation for the growing uterus, can affect the known clinical presentation of respiratory signs and symptoms. Adequate diagnosis and treatment of respiratory disease may be delayed [8,9]. In addition, it is recognized that pregnancy may increase the risk of severe influenza-associated complications [10,11].

It became clear throughout the 2009 H1N1 influenza pandemic [termed A (H1N1pdm09)] worldwide [12-17] that pregnant women were a highly vulnerable group. From July 2009 to January 2, 2010, it was reported that 44544 cases of the disease and 2051 deaths occurred in Brazil, [18]. However, it has been

estimated that the total number of cases and deaths were probably much higher than the notified number.

We proposed a novel approach to analyzing the burden of 2009 H1N1 influenza virus infection and other respiratory disease among patients with severe maternal morbidity. Cases with maternal outcomes complicated by severe respiratory disease were compared to cases with morbid conditions due to other causes (such as hemorrhage and hypertension). In addition, factors possibly associated with a higher risk of worse maternal outcome were evaluated by using the WHO standardized definitions of morbidity in 27 referral maternity hospitals.

Methods

The study evaluated severe maternal morbidity and near miss cases, from a prospective surveillance implemented in the Brazilian Network for Surveillance of Severe Maternal Morbidity, according to the 2009 WHO newly publicized criteria for these conditions [6]. The study complied with ethical principles guiding human research described in the Declaration of Helsinki and was approved by the Institutional Review Board of each local center and research coordinating center (CONEP 097/2009). The Informed Consent Form was waived, since data were obtained from hospital records after patient discharge, without any contact with research subjects.

The methodological details of the original study have already been published elsewhere [19]. Briefly, this multicenter study included 27 referral maternity hospitals distributed among the five Brazilian geographical regions. From July 2009 to June 2010, all women admitted to participating centers, who

were identified as having any life-threatening condition, near miss or maternal death, according to the WHO definition, were included in the study. Data collection was acquired through medical chart review after hospital discharge or death of the patient. Information was entered into the OpenClinica® electronic platform (version 2.5.5 - Waltham, MA, USA) through a structured form completed by the local coordinator from each participating center.

Quality control was carried out during various phases of the study. Initially, training was provided to the entire team participating in the study, using a detailed operations manual, with the definition of each variable. Meetings were held between the local research team and the coordinating team of the study to standardize data. Case review was conducted by the local investigator. Subsequently, the coordinating team of the study performed random reviews of manual and electronic forms for data consistency in visits to monitor the centers´ performance. Periodically, review of the electronic system was carried out to check for data inconsistency, along with systematic case review. Some reported conditions were delay or substandard care, which had been previously reported [20]. Reasons for the delay in treatment were the woman or family member, health service or health professional.

Sample size was determined by the prevalence of about 8 maternal near miss cases per 1000 births and a maternal mortality ratio of 140/100,000 live-born infants (95% confidence interval). It was predicted that 75000 births [19] needed to be monitored.

For the present analysis proposed, we considered severe respiratory disease as a suspected or confirmed case of influenza or acute respiratory

failure, defined as incapacity of the respiratory system to promote adequate gas exchange, with arterial blood gas parameters: PaO2 < 60 mmHg or peripheral saturation < 90%, associated or not with PaCO2 > 50 mmHg. Clinical parameters such as tachypnea (RR > 20) or bradypnea (RR <6), use of accessory respiratory muscles, nasal flaring, associated with torpor or agitation were also considered. For suspected or confirmed cases of A(H1N1)pdm09, case review was necessary to confirm whether laboratory tests had been performed with the results of these tests, since data in the original study had not been collected in detail. Case review was requested from each local center and new data were distributed into three groups: non-tested, positive and negative cases for A(H1N1)pdm09.

Initially, the prevalence of PLTC, MNM and MD was calculated per group, as well as the respective health indicators related to maternal morbidity and mortality: maternal near miss ratio, severe maternal outcome ratio, mortality index and maternal mortality ratio, according to the WHO definition [6]. To evaluate the progression of severe maternal morbidity in cases complicated by respiratory disease throughout the study, maternal outcomes (PLTC, MNM and MD) were measured for each month studied. The risk of severe maternal outcome associated with procedures used to manage the severity of conditions was estimated for the group with severe respiratory disease and other causes of severe maternal morbidity, through the Prevalence Ratios plus their respective 95%CI adjusted for the design effect of cluster sampling.

Subsequently, we performed an analysis considering the total number of cases with severe respiratory disease versus cases with other causes of severe

maternal morbidity. In each group, PLTC (less severe cases) and Severe Maternal Outcome (SMO: MNM + MD) cases were compared to evaluate the factors potentially associated with more severe disease, including delay in obstetric care, also using the Prevalence Ratios plus their respective 95%CI adjusted for the design effect of cluster sampling. The prevalence of sociodemographic, obstetric and perinatal factors were evaluated between the two groups using Chi-square tests. Values statistically significant were considered those with a p-value under 0.05. The statistical procedures for analysis were performed with SPSS and Stata.

Results

During the 12-month study period, 82388 women were monitored. Of these, 9555 had criteria for severe maternal morbidity. Among these 9555 women, only 485 (5%) had severe respiratory disease. However, in this group with respiratory illness, symptom severity progressed more rapidly, if compared to other causes of severe morbidity (Fig. 1), such as bleeding or hypertensive disorders, and may be 40 times more lethal.

Among the total number of women with respiratory disease, patients with suspected A(H1N1)pdm09 infection had more severe disease (55.2% MNM and 23.3% MD) than those without suspected A(H1N1)pdm09 (prevalence of MNM: 21.3%, MD: 14.1%) (Fig. 2). About 60% of cases of suspected A(H1N1)pdm09 were tested. Women who tested positive (49 cases) for A(H1N1)pdm09 had more severe disease, with a higher prevalence of SMO.

Figure 2 shows the distribution of cases with severe respiratory disease, according to progression of severity during the study period, based on date of

admission in participating centers. It is possible to observe a higher incidence of cases in the first months considered, especially July, August and September 2009. National guidelines and availability of vaccination during pregnancy were instituted in March/2010. Despite a downward trend in identifying PLTC, MNM and MM due to severe respiratory disease, pulmonary disorder remained an important cause during the entire period.

Considering health indicators, disease was more severe among cases tested and positive for A(H1N1)pdm09. Mortality rate was higher than 50% among positive cases for A(H1N1)pdm09. The death rate was about 36% in cases testing negative for A(H1N1)pdm09 and 27.5% in non-tested cases. In contrast, the mortality rate was only 7.4% in morbid disorders due to other causes. The maternal near miss to mortality ratio was 0.93:1, 1.80:1 and 2.39:1, among positive, negative and non-tested groups for A(H1N1)pdm09, respectively, compared to a value of 12.43:1 for other causes of severe maternal morbidity.

More than 55% of patients with severe respiratory disease had three diagnostic criteria for near miss: laboratory, clinical and management, while for the remaining causes of severe maternal morbidity, around 24% of patients only had criteria for laboratory or management diagnosis (Table 2). All procedures for management of severity were associated with a worse outcome in both groups, women with severe respiratory disease and those with severe maternal morbidity due to other causes (Table 3).

Analysis of sociodemographic and obstetric characteristics (Table 4) compared cases of PLTC and SMO for the group with severe respiratory

disease. It showed an association between non-white color, history of diabetes, low weight and use of drugs, in addition to delay in care. These were regarded as risk factors for more severe maternal outcome. In contrast, in the SMM group due to other causes, low maternal age, first pregnancy, history of maternal obesity and lack of a partner were identified as lower risk factors for worse maternal outcome (SMO), while hospitalization in a non-public institution, parity, history of caesarian section, drug abuse, occurrence at an earlier gestational age and mainly in the postpartum period, in addition to any type of delay in obstetric care, were associated with SMO (MNM and MD).

Concerning characteristics of pregnancy and perinatal results (Table 5), the group with severe respiratory disease had a higher rate of early preterm births, between 22-33 weeks of gestation, low birthweight, Apgar < 7 at five minutes of life, stillborn and the need for hospital admission/transference of the newborn infant, compared to the group with severe maternal morbidity due to other causes. Neonatal death increased threefold in women with severe respiratory disease. A marked difference was observed in the groups compared, when the mode of delivery and onset of labor were taken into consideration. The number of women who did not undergo pregnancy resolution during the severe morbid event was much higher in the respiratory disease group. Around 35% were “still pregnant” compared to 5% in the group with severe maternal morbidity due to other causes.

Discussion:

Our study presents the burden of severe respiratory diseases among cases of severe maternal morbidity and results of the 2009 H1N1 influenza pandemic, considering 27 referral maternity hospitals in Brazil. Overall, the prevalence of respiratory disease was rare (5%). Nevertheless, respiratory disease accounted for one-quarter of MNM cases and two-thirds of MD. Worse adverse outcomes occurred among cases of confirmed A(H1N1)pdm09 influenza, with an impressive MNM:MD ratio below one, meaning that there were more deaths than near miss cases in this group. Furthermore, the mortality index was over 50% in the A(H1N1)pdm09 group, compared to 7.4% for other causes of severe maternal morbidity. Mortality index correlates to quality of care. When the index is above 20%, it represents substandard care [21]. Our data also confirmed that the increased risk of SMO was linked to delays in health care (delays due to women/family members, health services or health professionals).

Studies have shown the impact of the 2009 H1N1 influenza A pandemic [A(H1N12009pdm)] on maternal health worldwide. Since then, there has been a clear change in clinical practice. There is a strong recommendation for vaccination during pregnancy and empirical antiviral therapy, as soon as possible in case of suspected disease [10]. Clinical evaluation determined treatment, in order to ensure timely and effective intervention. In our study, around 60% of suspected cases of A(H1N1)pdm09virus were tested. In accordance with previous reports, symptoms were more severe in positive cases [22]. The majority of cases in Brazil occurred during cold weather (July, August and September), period of increased infections by respiratory viruses

and influenza outbreak in the country (Brazil declared a pandemic in mid-July 2009).

Over half of the reported cases of severe respiratory disease were not due to suspected influenza infection. Acute respiratory failure was the cause, including a broad number of conditions, as follows: pulmonary edema, cardiac disease community-acquired pneumonia, aspiration, pulmonary embolism, asthma exacerbation or venous embolism. These complications include mostly indirect causes of maternal morbidity and mortality, which represent novel or preexisting health problems unrelated to pregnancy, such as cardiac disease and asthma. Asthma is the most common medical condition that may worsen during pregnancy. The prevalence of asthma in all pregnancies is 6-12% and it is often underdiagnosed and under-treated [9]. Direct causes of maternal morbidity and mortality can also lead to respiratory failure, such as systemic consequences of sepsis due to uterine infection and severe preeclampsia and eclampsia, complicated by pulmonary edema [23, 24].

The definitions of severe respiratory complications that are usually studied can be rather confusing and sometimes difficult to incorporate [25]. Recent onset of fever and respiratory symptoms, including cough is the clinical definition of Severe Acute Respiratory Syndrome. In the setting of an epidemic, this definition is very useful to raise awareness and ensure prompt treatment, as soon as a suspected case is identified [26]. ARDS is another acronym for Acute Respiratory Distress Syndrome, a different condition that represents hypoxemic respiratory failure and bilateral radiographic opacities, without congestive heart failure. This diagnosis depends on oxygenation deficit measurements and chest

imaging [27,28]. In the current study, we failed to accurately establish any of the above conditions, since we did not collect data on clinical symptoms (fever, cough) or obtain the results of those specific laboratory findings or imaging. Another limitation was the lack of data on the use of antiviral therapy or vaccination. For cases of SMO, complicated by documented organ dysfunction, ARDS would probably be the diagnosis of respiratory disease. Nevertheless, confirmation was lacking for all cases.

In general, the estimated risks for severe maternal outcome (SMO) in women with severe respiratory disease, factors associated with poor clinical progression (near miss or death), including non-white women, the history of diabetes, low weight and drug abuse, along with delay in care, contributed to a worse outcome for the majority of conditions under study. Drug abuse associated with increased risk of severity in cases of respiratory disease, is in agreement with previous reports [29,30]. Drug-related severe respiratory complications can occur, resulting from parenchymal (infectious and non-infectious pneumonitis, aspiration-related events, hemorrhage, pulmonary edema and pneumothorax), pulmonary vascular insults (endovascular infection, hemorrhage, and vasoconstriction) or airway (bronchospasm and hemorrhage) abnormalities. Diabetes was also associated with an increased risk of SMO among cases complicated by severe respiratory disease. Previous studies had clearly demonstrated this fact, even in the Brazilian population. Diabetes is one of the main risk factors for death from A(H1N1)pdm09 [31] virus infection.

Pregnancy characteristics and perinatal outcomes according to the main cause of severe morbidity showed that pregnancies complicated by respiratory

disease present an increased rate of preterm delivery and worse perinatal outcomes. This finding had already been demonstrated [10,32]. Studies have shown that vaccination during the first trimester of pregnancy can improve those outcomes and decrease stillbirth rates without increasing the risk of malformations, which is a common concern among health practitioners and pregnant women [33].

Conclusion

Severe respiratory disease, especially considering the influenza season, is one of the most serious causes of maternal near miss and death. Increased awareness of this condition, preventive vaccination during pregnancy, early diagnosis and treatment are required to improve maternal health.

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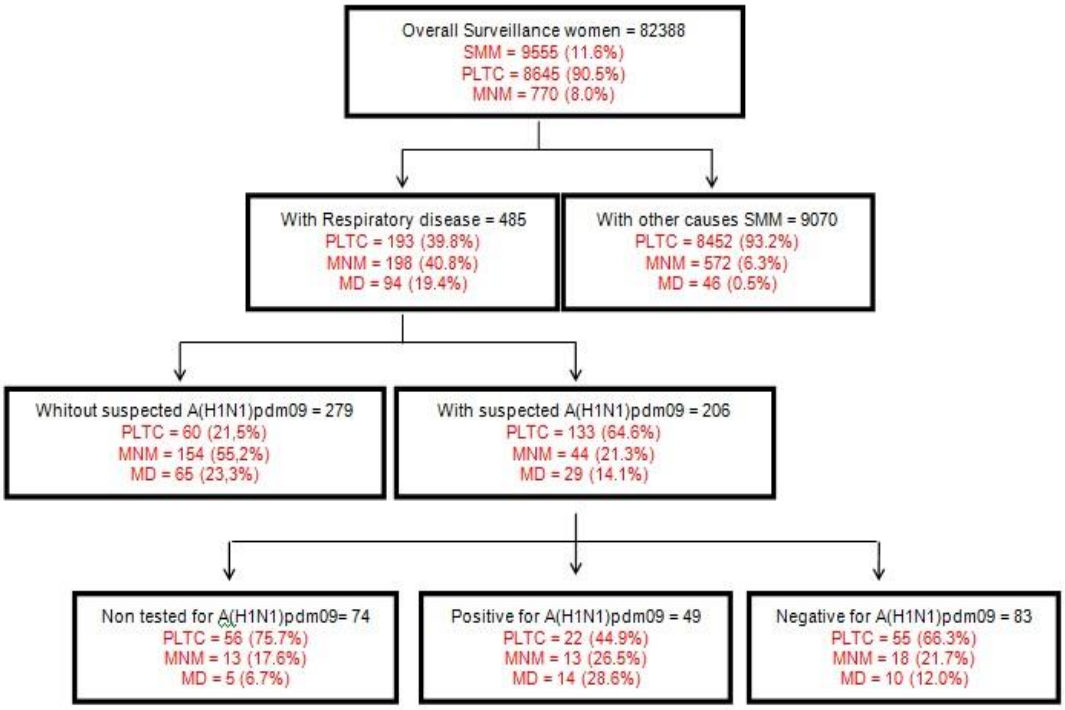
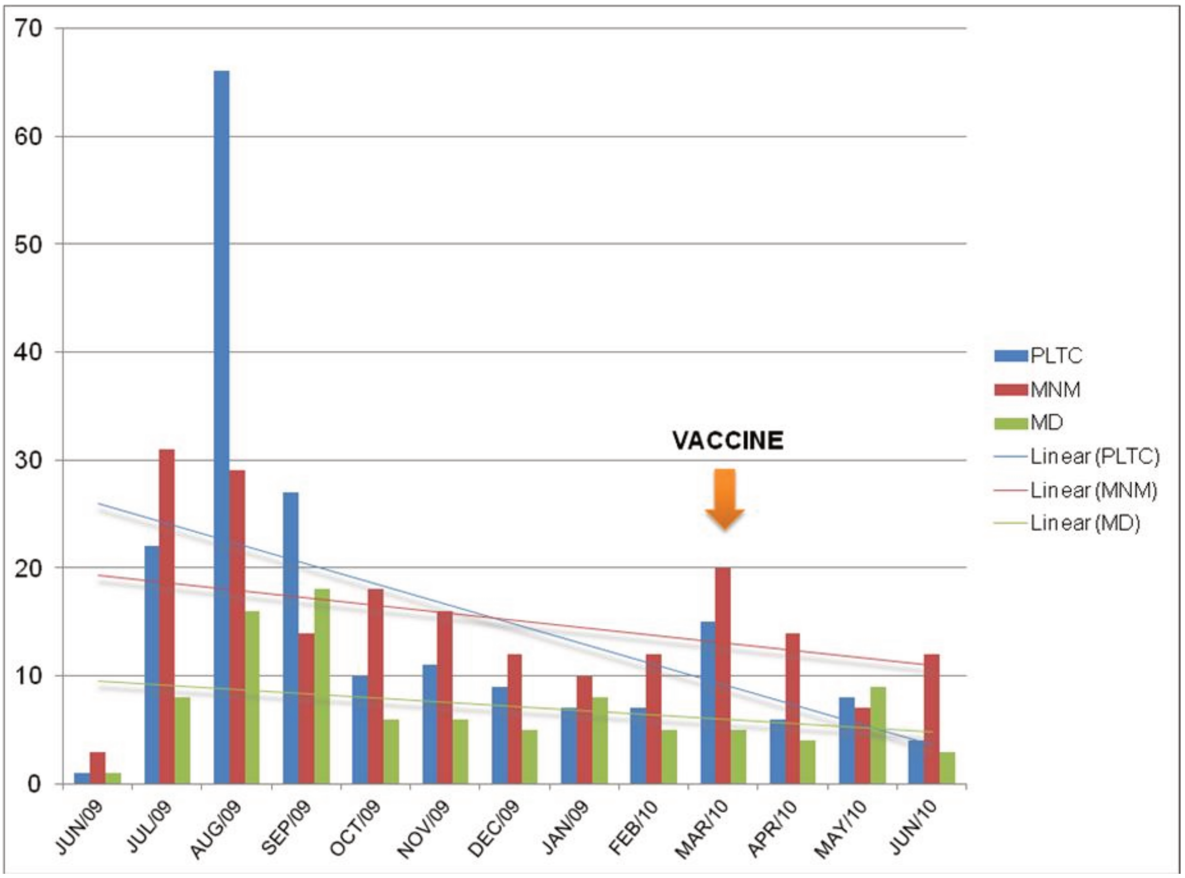


SMM: Severe Maternal Morbidity; PLTC: potentially life-threatening condition; MNM: maternal near miss; MD: maternal death.

Figure 1: Flow of women with severe maternal morbidity (SMM) due to suspected/confirmed A(H1N1)pdm09, considering Severe Respiratory Disease or other causes according to the final outcome in potentially life-threatening condition (PLTC), maternal near miss (MNM), or maternal death (MD).



PLTC: potentially life-threatening condition; MNM: maternal near miss; MD: maternal death.

Figure 2: Distribution of cases with severe respiratory disease according to progression of severity during the study period

Table 1. Women with severe respiratory disease: cases non-tested for influenza A(H1N1)pdm09, influenza A(H1N1)pdm09 positive, influenza A(H1N1)pdm09 negative and other causes of morbidity according to severity of outcome (PLTC, MNM, MD) and their correspondent health indicators

Conditions	PLTC	MNM	MD	Total	Health Indicators				
					MNMR/ 1000LB	SMOR/ 1000LB	MNM:MD ratio	Mortality index %	MMR/ 100000 LB
Influenza A(H1N1)pdm09 positive	22	13	14	49	0.16	0.33	**0.93:1**	**51.8**	17.0
Influenza A(H1N1)pdm09 negative	55	18	10	83	0.22	0.34	**1.80:1**	**35.7**	12.2
Non-tested for influenza A(H1N1)pdm09	116	167	70	353	2.03	2.89	**2.39:1**	**29.5**	85.2
Total Respiratory disease	193	198	94	485	2.41	3.55	**2.11:1**	**32.2**	114.4
Other causes	8452	572	46	9070	6.96	7.52	**12.43:1**	**7.4**	56.0

LB: 82.144

LB: live births; PLTC: potentially life-threatening condition; MNM: maternal near miss; MD: maternal death; MNMR: maternal near miss ratio; SMOR: severe maternal outcome ratio = (MNM+MD)/LB X 1000; MNM:MD ratio = MNM:1MD; Mortality index = MD/(MNM+MD); MMR: maternal mortality ratio = MD/LB X100.000.

Table 2 . Prevalence of maternal near miss criteria in women with severe respiratory disease or other causes of severe maternal morbidity

Maternal Near Miss criteria	Respiratory		Other causes		p *
	n	%	N	%	
					<0.001
Clinical only	20	6.8	93	15.0	
Laboratory only	21	7.2	151	24.4	
Management only	22	7.5	153	24.8	
Clinical + Laboratory	15	5.1	23	3.7	
Clinical + Management	41	14.0	82	13.3	
Laboratory + Management	12	4.1	30	4.9	
Clinical + Laboratory + Management	161	55.1	86	13.9	

* Adjusted for design effect of cluster sampling

Table 3. Estimated risk of severe maternal outcome (SMO) among women with severe respiratory disease or other causes of severe maternal morbidity according to management procedures used for severity

Procedures associated with severity	Respiratory		PR	95% CI *	Other causes		PR	95% CI *
	SMO	PLTC			SMO	PLTC		
Blood transfusion	146	13	**2.05**	**1.38 – 3.05**	397	1010	**9.78**	**7.26 – 13.18**
Central venous access	190	11	**2.63**	**1.71 – 4.06**	125	37	**13.94**	**10.30 –18.88**
ICU admission	262	75	**3.84**	**1.94 – 7.59**	364	1414	**5.88**	**3.44 – 10.05**
Hospital stay >7days	211	65	**1.97**	**1.32 – 2.95**	322	2270	**2.72**	**1.84 – 4.03**
Invasive mechanical ventilation	204	1	**3.17**	**2.08 – 4.81**	86	5	**15.95**	**11.85 –21.48**
Use of vasoactive drug	148	0	**2.34**	**1.60 – 3.43**	96	0	**17.19**	**12.90 –22.90**
Transfusion of ≥5U packed red blood cells	60	0	**1.83**	**1.37 – 2.45**	189	0	**20.70**	**16.15 –26.53**
Intubation and ventilation ≥60 min not related with anesthesia	210	0	**3.35**	**2.23 – 5.05**	85	0	**16.86**	**12.70 –22.37**
Dialysis for acute renal insufficiency	34	0	**1.75**	**1.35 – 2.26**	29	0	**15.35**	**11.52 –20.46**
CPR	84	0	**1.93**	**1.46 – 2.55**	36	0	**15.52**	**11.66 –20.67**

SMO: severe maternal outcome (maternal near miss plus maternal death); PLTC: potentially life-threatening condition; PR: prevalence ratio adjusted for cluster design effect; CI: confidence interval; ICU: intensive care unit; CPR: Cardiopulmonary resuscitation

* Adjusted for design effect of cluster sampling

Values in bold mean they are statistically significant ($p<0.05$)

Table 4. Estimated risk of severe maternal outcome (SMO) among women with severe respiratory disease or other causes of severe maternal morbidity according to sociodemographic and obstetric characteristics, medical history and delay in care

Variables	Respiratory		PR	95% CI *	Other causes		PR	95% CI *
	SMO	PLTC			SMO	PLTC		
Age (years)								
≤ 19	59	33	1.11	0.90 – 1.38	80	1541	**0.73**	**0.59 – 0.89**
20 – 34	176	130	1.00		401	5513	1.00	
≥ 35	57	30	1.14	0.97 – 1.34	137	1398	**1.32**	**1.05 – 1.64**
Marital status [a]								
With partner	152	100	1.00		317	3704	1.00	
Without partner	84	57	0.99	0.76 – 1.28	159	3466	**0.56**	**0.40 – 0.78**
Education [b]								
Elementary	91	62	1.00		192	2871	1.00	
>Elementary	89	62	0.99	0.77 – 1.28	188	3368	0.84	0.66 – 1.08
Skin Color [c]								
White	133	112	1.00		247	2539	1.00	
Non white	115	62	**1.20**	**1.01 – 1.41**	229	3702	0.66	0.43 – 1.01
Number of pregnancies [d]								
1	117	65	1.12	0.92 – 1.38	194	3599	**0.65**	**0.56 – 0.75**
2 or more	170	127	1.00		411	4810	1.00	
Number of Childbirths [d]								
0	132	74	1.00		210	4160	1.00	
1 or more	155	118	0.89	0.73 – 1.08	395	4249	**1.77**	**1.55 – 2.02**
Previous C-sections [e]								
0	217	129	1.00		402	6363	1.00	
1 or more	61	63	0.78	0.59 – 1.04	184	1940	**1.46**	**1.22 – 1.74**
Medical history [f]								
Chronic hypertension	30	17	1.11	0.88 – 1.41	84	1325	0.90	0.66 – 1.23
Diabetes	12	3	**1.39**	**1.04 – 1.86**	21	173	1.69	0.94 – 3.07
Smoking	21	23	0.80	0.58 – 1.12	32	390	1.18	0.68 – 2.04
Obesity	39	36	0.88	0.68 – 1.12	66	1848	**0.46**	**0.30 – 0.70**
Low weight	5	0	**1.73**	**1.33 – 2.27**	1	21	0.70	0.09 – 5.30
Respiratory disease	26	31	0.76	0.48 – 1.20	11	166	0.96	0.62 – 1.46
HIV/AIDS	9	9	0.85	0.51 – 1.44	6	67	1.27	0.56 – 2.88
Drug abuse	14	4	**1.36**	**1.06 – 1.74**	11	71	**2.09**	**1.20 – 3.63**
Prenatal coverage [g]								
Public	206	134	1.00		430	5890	1.00	
Other	34	15	1.15	0.85 – 1.54	69	746	1.24	0.82 – 1.88
Prenatal adequacy [h]								
No	56	36	1.00	0.81 – 1.22	109	1925	**0.75**	**0.60 – 0.94**
Yes	212	135	1.00		476	6197	1.00	
Hospitalization coverage [i]								
Public	285	187	1.00		602	8366	1.00	
Other	6	6	0.83	0.44 – 1.54	16	78	**2.54**	**1.43 – 4.50**

Gestational age at hospital admission [j]								
<22	36	42	0.72	0.50 – 1.02	47	406	**3.36**	**1.77 – 6.37**
22 – 36	161	117	0.90	0.69 – 1.17	297	3604	**2.47**	**1.70 – 3.58**
≥37	38	21	1.00		125	3926	1.00	
Postpartum	51	12	1.26	0.97 – 1.63	124	290	**9.71**	**6.20 –15.20**
Delays								
Women/family members [k]	124	53	**1.42**	**1.11 – 1.82**	218	2902	1.14	0.89 – 1.44
Health service [l]	109	12	**1.85**	**1.36 – 2.51**	166	1089	**2.35**	**1.66 – 3.33**
Health professional [m]	112	9	**1.93**	**1.47 – 2.55**	167	1260	**2.07**	**1.41 – 3.04**
Any delays [n]	213	63	**2.39**	**1.60 – 3.56**	367	4044	**1.74**	**1.36 – 2.24**

SMO: severe maternal outcome (maternal near miss plus maternal death); PLTC: potentially life-threatening condition; PR: prevalence ratio adjusted for cluster design effect; CI: confidence interval; ICU: intensive care unit;

* Adjusted for design effect of cluster sampling

Values in bold mean that they are statistically significant ($p<0.05$)

Missing information for: a: 92 and 1,424 (respiratory and other causes); b: 181 and 2,451; c: 63 and 2,353; d: 6 and 56; e: 15 and 181; f: 43 and 1,271; g: 96 and 1,935; h: 46 and 363; i: 1 and 8; j: 7 and 251; k: 71 and 1,104; l: 15 and 692; m: 17 and 607; n: 39 and 800 cases.

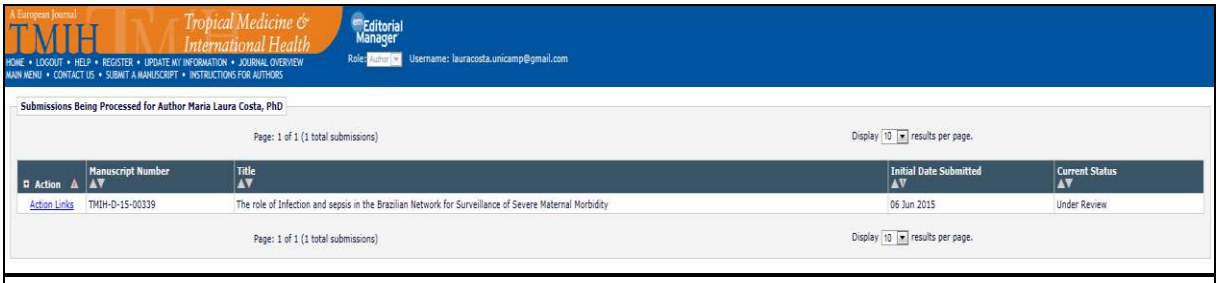
Table 5. Characteristics of pregnancy and perinatal results according to cause of morbidity: severe respiratory disease or other causes

Variables	Respiratory		Other causes		p *
	n	%	n	%	
Gestational age at delivery (weeks) [a]					**<0.001**
<22	20	4.5	307	3.6	
22 – 27	23	5.2	259	3.0	
28 – 33	83	18.8	1341	15.6	
34 – 36	56	12.7	1724	20.1	
≥37	95	21.5	4427	51.7	
Still pregnant	164	37.2	511	6.0	
Mode of delivery [b]					**<0.001**
Vaginal	58	12.1	2080	23.0	
C-section	233	48.5	5921	65.5	
Abortion/ ectopic pregnancy	24	5.0	521	5.8	
Still pregnant	165	34.4	512	5.7	
Onset of labor [c]					**<0.001**
Spontaneous	66	14.1	2652	29.6	
Induction	33	7.1	792	8.8	
No labor	179	38.3	4477	50.0	
Abortion	24	5.1	521	5.8	
Still pregnant	165	35.3	513	5.7	
Perinatal results					
Apgar at 5 min <7 [d]	38	17.7	258	3.5	**<0.001**
Apgar at 5 min ≥7	177	82.3	7152	96.5	
Birth weight <2500g [e]	142	58.9	3007	39.1	**<0.001**
Birth weight ≥2500g	99	41.1	4675	60.9	
Still birth [f]	36	13.6	352	4.5	**<0.001**
Live birth	229	86.4	7504	95.5	
Perinatal outcome [g]					**<0.001**
Neonatal death	15	7.0	178	2.5	
Admitted/ transferred	83	38.6	1547	21.4	
Hospital discharge	117	54.4	5506	76.1	

* Adjusted for design effect of cluster sampling
Missing information for: a: 545; b: 41; c: 133; d: 1,930; e: 1,632; f: 1,434; g: 2,109 cases

3.2. Artigo 2

Pfitscher LC, Cecatti JG, Haddad SM, Parpinelli MA, Souza JP, Quintana SM, Surita FG, Costa ML, for the Brazilian Network for Surveillance of Severe Maternal Morbidity study group. The role of infection and sepsis in the Brazilian Network for Surveillance of Severe Maternal Morbidity. *Tropical Medicine & International Health* 2015 (Submitted).



Tropical Medicine & International Health

The role of Infection and sepsis in the Brazilian Network for Surveillance of Severe Maternal Morbidity

--Manuscript Draft--

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Full Title:	The role of Infection and sepsis in the Brazilian Network for Surveillance of Severe Maternal Morbidity
Article Type:	Original Research Paper
Keywords:	maternal morbidity; maternal mortality; maternal near miss; sepsis; infection.
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Original Research

The role of infection and sepsis in the Brazilian Network for Surveillance of Severe Maternal Morbidity

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Running title: Infection and Maternal Morbidity

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Abstract

Objective: to identify the burden of severe infection within the Brazilian Network for Surveillance of Maternal Morbidity and factors associated with worse maternal outcomes.

Methods: This was a multicenter cross-sectional study, involving 27 referral maternity hospitals in Brazil. The WHO´s standardized criteria for potentially life threatening conditions (PLTC) and maternal near miss (MNM) was used to identify cases through prospective surveillance and the main cause of morbidity was identified as infection or other causes (hypertension, hemorrhage or clinical/surgical). Complications due to infection were compared to complications due to the remaining causes of morbidity. Factors associated with a severe maternal outcome (SMO) were accessed for the cases of infection.

Results: Among 9555 cases of severe maternal mordidity, 502 (5.3%) cases of maternal morbidity were associated with severe infection against 9053 cases (94.7%) of other causes. Considering increased severity of cases, infection was responsible for one fourth of all MNM and nearly half of maternal deaths (MD), with a MNM:MD ratio three-fold higher then cases without infection. Within cases of infection, substandard care was present in over half of the SMO cases. Factors independently associated with worse maternal outcomes included: HIV/AIDS, hysterectomy, prolonged hospitalization, intensive care admission and delays on medical care.

Conclusions: infection remains an alarming cause of maternal morbidity and mortality and timely diagnosis and adequate management of cases are key to improving outcomes during pregnancy. Delays should be addressed, risk factors identified, and specific protocols of surveillance and care developed for use during pregnancy.

Keywords: severe acute maternal morbidity; maternal mortality; maternal near miss; sepsis; infection.

Introduction

The overall burden of infection and its progression to sepsis, in different populations, causing increased risk of morbidity and mortality is in focus worldwide; with the identification of different accountable pathogens and systemic response pathways, especially during pandemic crises (1-3). Severe infection during pregnancy is a serious concern in high, low and middle-income countries, with inherent difficulties towards the identification and management of infection. For example, physiological changes experienced during pregnancy, such as tachycardia, tachypnea, hypotension and increased white blood count, can mimic some of the expected responses to an infection and delay the recognition of the infection and its severity (4-8). The immunological mechanisms involved and possibly responsible for susceptibility to infection are not fully understood. However, we now know the idea of pregnancy as a period of immune suppression is simplistic and responses towards an infection depend on the integrative communication of maternal and fetal-placental immune systems towards specific pathogens (6).

Standardized definitions for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock were initially published in 1992 (9). The main rationale was to consider a continuum of severity, in which severe sepsis accounts for confirmed infection complicated by organ dysfunction, infection-induced hypotension or tissue hypoperfusion (5, 10). However, there

are no specific criteria for the definition of severe sepsis during gestation. Pregnancy-associated severe sepsis (PASS) is a rare, yet increasing, complication worldwide. Indeed, studies have shown that it is among the leading causes of preventable maternal mortality in low and high-income countries (8, 11, 12). However, data collection and evaluation are not standard between studies, the range of incidence rates worldwide are broad, and most evaluations are retrospective with restricted sample sizes, most have unclear definitions of sepsis and of selected phases of pregnancy outcomes (12). If one considers middle and low-income scenarios, data on the burden of severe infection on pregnancy outcomes is largely unknown.

Maternal death or maternal mortality (MM) is considered one of the most significant indicators of global health inequities. Importantly, for each case of death there are a number of women that suffer severe complications. Thus, the use of severe maternal morbidity instead of MM, as an indicator for severe complications during pregnancy and childbirth, has advantages including enlarging the number of cases available for study and better information because women are still alive and able to provide the relevant information (13, 14). In 2009, the World Health Organization (WHO) published a standard definition and criteria for maternal morbidity (15), allowing uniform data collection and improved comparisons between studies.

From a potentially life threatening condition (PLTC), defined by 26 proposed severity markers, to a very severe condition with organ disfunction and/or failure called maternal near miss (MNM), clear definitions are provided by the WHO. A woman with one of these established laboratory, clinical or

management intervention criteria is considered a MNM case and, from a theoretical perspective, the MNM cases should be as similar to maternal deaths as possible, with the assumption that women survive because of timely interventions or just good fortune (15).

This study evaluates the role of severe infection and other factors for their roles in worse maternal outcomes. Data were collected from the Brazilian Network for Surveillance of Severe Maternal Morbidity, a multicenter study including prospective data collection from 27 referral maternity hospitals in Brazil, using the framework of severe maternal morbidity defined by the WHO.

Material and Methods:

The current study is a secondary analysis of the Brazilian Network for Surveillance of Severe Maternal Morbidity: a multicenter cross-sectional study, implemented in 27 maternity hospitals in all 5 regions of Brazil. During a one-year period, a prospective surveillance was conducted to identify cases of Potentially Life Threatening Condition (PLTC), Maternal Near Miss (MNM) and Maternal Death (MD) in these facilities, according to standardized WHO criteria (15). Details on the study methods were published previously (16).

The study was approved by the National Council for Ethics in Research and also by each center´s Institutional Review Board prior to the beginning of data collection - Letter of approval 097/2009. All principles defined by the Brazilian National Health Council and the Helsinki Declaration regulating research on human beings were followed. A waiver of individual informed consent was granted, as data collection occurred post hospital discharge or post mortem, with no personal contact with study subjects.

Briefly, a trained research team within each facility was responsible for data collection from all women admitted during pregnancy, childbirth or the postpartum period who had any of the criteria for severity conditions defined by the WHO. Information on eligible cases were obtained from the review of medical charts into a specific coded form and after data was transferred to electronic forms using an online platform (OpenClinica® version 2.5.5 - Waltham, MA, USA). The main complication in the chain of events leading to the severe morbidity was accessed (infection, hypertension, hemorrhage or clinical-surgical) and detailed information on the maternal outcome obtained. There was strict quality control, with preparatory meetings including all investigators, detailed manual of operations and site visits to each of the centers with a random selection of cases for evaluation of systematic consistency by local investigators and by the coordinating center. Finally, a computerized search for inconsistencies in the database was performed, with a set of validation/cross-checking rules as part of online data management.

We assessed the burden of severe infection within the Brazilian Network for Surveillance of Severe Maternal Morbidity, comparing these cases to other causes of morbidity (hypertensive, hemorrhagic, clinical/surgical). The operational definition of infection cases considered variables initially defined for the main study: severe sepsis (confirmed infection with organ dysfunction or irresponsive hypotension), meningitis and suspected or confirmed cases of Influenza A(H1N1)pdm09. Initially, the prevalence of PLTC, MNM and MD was calculated and compared between the two groups (infection compared to other causes of morbidity). The following health indicators related to maternal

morbidity and mortality were estimated: the maternal near miss incidence ratio (MNM incidence ratio), Severe Maternal Outcome ratio (SMOR, MNM+MD), maternal near miss to maternal death ratio (MNM:MD ratio), mortality index and maternal mortality ratio (MMR), according to WHO recommendations (15).

All cases of infection were then assessed for their maternal outcomes according to the main site of infection (uterine, pulmonary, urinary or other). In order to evaluate sociodemographic and obstetric factors possibly related to the worse maternal outcomes and increasing severity among women with infection, two groups were compared: one with potentially life threatening conditions (PLTC) and the other with severe maternal outcomes (SMO=MNM+MD). The prevalence ratios (PR), with their respective 95% confidence intervals (CI) adjusted for the cluster effect (17), were then estimated. The variables evaluated consisted of several maternal characteristics, obstetric and medical history, characteristics of the current pregnancy and delays in obstetric care. The approach for defining substandard care or delays was previously reported (18) and accounted for delays related to the women or family member, health service and health professional.

The diagnostic criteria considered for identifying maternal morbidity and the conditions of severity management and perinatal outcomes were assessed comparing the two groups (PLTC and SMO) with estimated PR with its 95% CI adjusted for the cluster effect. Finally, a multiple Poisson regression analysis was used to identify the factors independently associated with greater severity of complications due to infection, including all possible predictors in the model of analysis.

Sample size was determined as described previously (16). Briefly, it was based on the expected need of screening 75,000 deliveries in order to identify around 100 maternal deaths and 600 maternal near miss cases (according to an estimated prevalence of around eight cases of NM for every 1,000 deliveries (19), a maternal mortality ratio of 140 for every 100,000 live births, and a confidence level of 95%).

Results:

During the study period, 82,388 delivering women were screened, which included 9555 cases of severe maternal morbidity (PLTC and MNM) and MM. Of these 9555 cases, the main cause of morbidity was identified (Table 1). In 502 (5.3%) cases severe maternal morbidity was associated with severe infection (294 cases of severe sepsis, 206 cases of confirmed or suspected influenza A (H1N1)pdm09 and only 2 cases of meningitis) with 9053 cases (94.7%) associated with other (non-infectious) causes (hypertension, hemorrhage or clinical/surgical complications). Considering increasing severity, infection was responsible for around one fourth of all MNM and almost half of the cases of MD (Table 1).

In order to evaluate the extent of severity, comparing cases with infection as the main cause of morbidity with cases complicated by other causes of morbidity, the health indicators according to the WHO definition of severe maternal morbidity were assessed (Table 1). The MNM incidence ratio was of 2.2/1000 live births (LB) among women with infection as main condition of severity and 7.2/1000 LB among the remaining cases; the severe maternal outcome ratio (SMOR) was 3.0/1000 LB among the infection cases and

8.1/1000 LB among the non-infectious cases. The MNM:MD ratio also showed a marked difference between groups: 2.8:1 for the infection cases and 7.8:1 for the remaining cases. The mortality index was 26.3% for infection cases and 11.3% for cases without infection as main cause of morbidity.

Considering the main site of infection reported on the medical charts (Table 2), pulmonary was the most prevalent (52.8%), followed by uterine (22.5%) and urinary (16.6%). When evaluating severity, urinary site of infection accounted for most of SMO cases (Table2).

In order to address factors possibly associated to a worse maternal outcome among cases complicated by infection, bivariate analysis was performed comparing cases of severe maternal outcome and cases of potentially life threatening condition among (Table 3). Age, skin color, education, marital status, number of pregnancies and of childbirths, previous C-sections and medical history were not significantly associated to a worse outcome. However, age range between 30-39 years presented a significant protective effect towards greater severity (SMO). Several preexisting medical conditions: diabetes, cancer, drug abuse and underweight, presented increased estimated risk for a worse prognosis (SMO).

We also estimated risk of SMO among women with severe infection during pregnancy or childbirth, according to the characteristics of their current pregnancy and delays in obstetric care (Table 4). Prematurity, regardless of gestational age (22-36 weeks of pregnancy), was significantly associated with worse maternal outcomes. Considering access to referral center, spontaneous search for care was found to be a protective factor against the occurrence of

severe complications due to infection. When considering delays in obstetric care, it is important to note that over half of the women evaluated with SMO presented some kind of substandard care in comparison to 40% in those who had PLTC (Table 4). Delays related to health service were most frequent.

As expected, all of the assessed management procedures of severity, especially intensive care unit admission, central venous access and invasive mechanical ventilation, were most prevalent among the SMO cases (Table 5), with significant association towards worse maternal outcome (MNM or MD). The analysis of perinatal outcomes showed that a five minute Apgar score of below 7, low birth weight, and stillbirth, were all more frequent among severe cases (SMO) and were significantly associated to increased risk of severity.

As shown in table 6, multivariate analysis identified that, among the factors evaluated simultaneously, the following were independently associated with a SMO in women with severe infection: hysterectomy, central venous access, prolonged hospital stay, medical history of HIV/AIDS, intense care unit (ICU) admission, delays on medical care related to the health system, intubation/ventilation for over 60 minutes not related to anesthesia and use of continuous vasoactive drugs. Other major surgical procedure (mainly abscess drainage) presented a protective effect towards severity of outcome.

Discussion

The main finding of this study is that infection provides a significant burden upon severely ill pregnant women. Although prevalence of infection is low (5.3%), it accounted for one fourth of the total MNM and almost half of MD cases. The use

of health indicators to understand these numbers is helpful, with the MNM:MD ratio indicating the infection cases being nearly 3-fold higher risk of death than for the remaining causes of morbidity considered.

Another important indicator considered is the Mortality Index (MI). This number correlates to the quality of care provided. High levels (over 20%) indicate inadequate quality of obstetric care. High-income countries can present a MI as low as 2% (20). In our study, for cases of infection the MI was around 26% and 11% for the remaining causes of morbidity. This reflects the occurrence of substandard care in our setting when evaluating the role of infection in maternal morbidity, which can influence the observed outcomes. Prompt diagnosis and timely management of this complication determines the possibility for enhanced prognosis (5). The MI can justify government investments towards adequate provision of care, in order to diminish maternal morbidity and mortality and to improve outcomes of pregnancy. Understanding the occurrence of delays in care (18) and how to overcome them can certainly also contribute to improved maternal outcomes in cases of infection. Another relevant consideration would be the development of guidelines for sepsis management specific to pregnancy.

In Brazil, a middle-upper income country, with a current Maternal Mortality ratio of around 58:100,000 LB (Live Births), the direct causes of maternal deaths, especially hypertensive disorders, hemorrhage and infection of uterine/obstetrical etiology are the leading etiologies identified (21). However, there has been a clear shift towards increasing prevalence of indirect causes, a

change reported worldwide and recently described as an obstetrical transition process (22).

Indirect maternal mortality accounts for pregnancy-related death in a woman with a pre-existing or newly developed health problem not related to gestation, such as cardiac disease, HIV/AIDS, chronic hypertension, anaemia, cerebro-vascular disease or infections (such as pyelonephritis and influenza-like illness). In the data presented here, when analyzing site of infection, the great numbers of indirect causes, due to pulmonary complications likely are a consequence of the influenza H1N1 pandemic in the year (H1N1 pdm09) (23) of data collection (2009), with over 200 reported cases in our sample and around 30 MD (results not shown). Recent studies have shown that the use of adequate guidelines, awareness, and preventive measures with influenza vaccines have great impact, especially in individuals at increased risk, such as pregnant women (24-26).

Our analysis of socio-demographic characteristics associated to severity mostly did not present results similar to previous published literature on risk factors for the development of PASS (12), with none significantly associated to more severe maternal outcomes. This may be to different patient populations: our baseline population was of severe morbidity, and the comparison was between PLTC and SMO. Another consideration is that most studies address sepsis and severe sepsis while we considered a broader approach for analyzing infection. The result of age range 30-39 years as being protective from SMO was unexpected, and perhaps was due to the restricted number of these cases.

Though, for age over 40 years there was a trend towards worse outcome, in accordance to previous published data (8), but was not statistically significant.

The evaluation of gestational age at delivery showed that between 22 and 36 weeks of gestation, women with severe morbidity and infection were at increased risk for a worse outcome (SMO). Prematurity is one of the main concerns when considering maternal health (27), and could be cause or consequence of a severe infectious complication. Our study cannot determine causality; nevertheless, this finding is important as prematurity has great impact for individuals future health and for the society. The result of gestational age under 22 weeks with no significant association towards severity may reflect the decrease in the numbers of unsafe abortion and increased use of misoprostol in our scenario (28).

Our multivariate analysis identified factors independently associated with SMO in women with infection, in accordance to previous findings (8, 11). For the listed management criteria of severity, as expected, interventions were more related to the increased severity. The only protective factor was “other major surgical procedures”, which represented mostly, in our sample, abscess drainage, an intervention that can have an effect in controlling infection (29), especially after complications due to a surgical procedure (such as C-section, which was quite high in our study).

For this study, we considered that the best approach to undertake the role of infection would be to include cases complicated by severe sepsis, meningitis and suspected or confirmed influenza A(H1N1)pdm09. These were the variables initially defined for the main study (16), related to the diagnosis of infection.

There are limitations to consider, such as lacking data on results of cultures (for identifying the agent of infection), antibiotic use, clinical features and signs at diagnosis and the timing of events. There is also the difficulty of evaluating causality and defining the underlying risk factors for the considered infection. However, this study has novel findings: we use severe maternal morbidity according to the WHO definition, have a large sample size from a middle-income country, and have data on complications during all pregnancy (with no restriction on gestational age at admission) and postpartum, with systematic prospective data collection.

In conclusion, severe infection remains as an alarming cause of maternal morbidity and mortality and timely diagnosis and management of this complication are vital towards improved outcomes during pregnancy and the postpartum period. Delays in healthcare should be addressed, risk factors identified, and specific protocols of healthcare and surveillance developed for this singular period of a women´s life.

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Table 1. Outcome of maternal complications due to infectious and non-infectious underlying medical conditions and their correspondent health indicators among women with severe maternal morbidity in Brazil

Maternal Outcome	Condition Infection	Condition Non-infectious
Total	502 (5.3%)	9053 (94.7%)
Potentially Life Threatening Condition (PLTC)	255 (2.9%)	8390 (97.1%)
Maternal Near miss (MNM)	182 (23.6%)	588 (76.4%)
Maternal Death (MD)	65 (46.4%)	75 (53.6%)
Health Indicators (LB*: 82.144)		
Maternal Near-Miss Ratio (MNMR)	2.2/1000 LB	7.2/1000 LB
Severe Maternal Outcome Ratio (SMOR)	3.0/1000 LB	8.1/1000 LB
Maternal Near-Miss Mortality Ratio (MNM:MD ratio)	2.8:1	7.8:1
Mortality Index (MD/(MNM+MD)	0.263=26.3%	0.113=11.3%

*LB=Live Births

Table 2 Maternal outcome according to the main site of infection among women with infection as main cause of severe maternal morbidity in Brazil

Main site of infection ●	SMO	PLTC	Total #
Uterine	54 (48.6%)	57 (51.4%)	111 (22.5%)
Pulmonary	119 (45.6%)	142 (54.4%)	261 (52.8%)
Urinary	46 (56.1%)	36 (43.9%)	82 (16.6%)
Other *	21 (52.5%)	19 (47.5%)	40 (8.1%)
Total	240 (48.6%)	254 (51.4%)	494 (100%)

SMO = Severe Maternal Outcome (maternal near miss plus maternal death); PLTC = Potentially Life-Threatening Condition

●12 cases had more than one site of infection and were categorized by the main site.

There was lack of information about the site for eight cases.

*Other site of infection: wound, abdominal, blood vessel.

Table 3. Estimated risks of severe maternal outcome (SMO = MNM+ MD) among women with severe infection and sepsis during pregnancy or childbirth according to maternal characteristics, obstetric and medical history

Predictors	SMO		PLTC		PR	95% CI
	n	%	n	%		
Age (years)						
≤ 19	52	49.5	53	50.5	0.95	0.72 – 1.26
20 - 29	131	52.0	121	48.0	1.00	Ref.
30 - 39	46	38.7	73	61.3	**0.74**	**0.59 – 0.93**
≥ 40	18	69.2	8	30.8	1.33	0.95 – 1.87
Skin Color						
White	112	44.6	139	55.4	1.00	Ref.
Non white	100	50.3	99	49.7	1.13	0.95 – 1.33
Education						
Elementary	80	52.6	72	47.4	1.21	0.94 – 1.56
>Elementary	75	43.4	98	56.6	1.00	Ref.
Marital status						
With partner	136	52.1	125	47.9	1.00	Ref.
Without	67	43.5	87	56.5	0.83	0.59 – 1.19
Number of pregnancies						
1	99	50.0	99	50.0	1.06	0.81 – 1.39
2-3	88	47.3	98	52.7	1.00	Ref.
4 or more	57	50.0	57	50.0	1.06	0.83 – 1.34
Number of childbirths						
0	107	49.5	109	50.5	1.05	0.80 – 1.39
1 -2	95	47.0	107	53.0	1.00	Ref.
3 or more	42	52.5	38	47.5	1.12	0.86 – 1.45
Previous C-sections						
0	184	51.1	176	48.9	1.00	Ref.
1 or more	56	42.4	76	57.6	0.83	0.62 – 1.11
Medical history						
Chronic hypertension	20	54.1	17	45.9	1.18	0.91 – 1.53
Diabetes	14	82.4	3	17.6	**1.82**	**1.33 – 2.49**
Kidney disease	12	70.6	5	29.4	1.55	0.90 – 2.65
Collagen disorders	2	40.0	3	60.0	0.86	0.43 – 1.71
Heart disease	10	38.5	16	61.5	0.82	0.46 – 1.46
Smoking	21	42.0	29	58.0	0.89	0.68 – 1.17
Obesity	30	44.1	38	55.9	0.94	0.63 – 1.40
Low weight	4	100.0	0	00.0	**2.17**	**1.71 – 2.75**
Sickle cell	4	66.7	2	33.3	1.44	0.64 – 3.25
Respiratory disease	14	37.8	23	62.2	0.80	0.43 – 1.49
HIV/AIDS	9	52.9	8	47.1	1.14	0.81 – 1.62
Thyroid disease	7	63.6	4	36.4	1.38	0.75 – 2.53
Neurologic disease	4	36.4	7	63.6	0.78	0.35 – 1.71
Cancer	4	80.0	1	20.0	**1.73**	**1.15 – 2.62**
Drug abuse	12	75.0	4	25.0	**1.65**	**1.16 – 2.34**

SMO = Severe Maternal Outcome (maternal near miss plus maternal death); PLTC = Potentially Life-threatening Condition; PR = prevalence ratio adjusted for cluster effect; CI = confidence interval.
Values in bold mean they are statistically significant

Table 4. Estimated risks of severe maternal outcome (SMO = MNM + MD) among women with severe infection and sepsis during pregnancy or childbirth according to characteristics of current pregnancy and delays in obstetric care

Predictors	SMO		PLTC		PR	95% CI
	n	%	n	%		
Prenatal coverage						
Public	180	50.8	174	49.2	1.00	Ref.
Other	62	49.6	63	50.4	0.98	0.69 – 1.38
Prenatal adequacy						
No	39	48.1	42	51.9	0.96	0.74 – 1.23
Yes	186	50.4	183	49.6	1.00	Ref.
Hospitalization coverage						
Public	241	49.2	249	50.8	1.00	Ref.
Other	5	45.5	6	54.5	0.92	0.51 – 1.69
Gestational age at hospital						
< 22	37	41.1	53	58.9	0.97	0.56 – 1.68
22 - 27	48	54.5	40	45.5	1.29	0.80 – 2.07
28 - 33	57	50.0	57	50.0	1.18	0.80 – 1.75
34 - 36	26	45.6	31	54.4	1.08	0.69 – 1.69
≥ 37	22	42.3	30	57.7	1.00	Ref.
Postpartum	51	58.0	37	42.0	1.37	0.85 – 2.21
Gestational age at delivery						
< 22	17	48.6	18	51.4	1.19	0.64 – 2.21
22 - 27	15	75.0	5	25.0	**1.84**	**1.13 – 2.99**
28 - 33	59	75.6	19	24.4	**1.85**	**1.25 – 2.74**
34 - 36	33	71.7	13	28.3	**1.76**	**1.20 – 2.57**
≥ 37	40	40.8	58	59.2	1.00	Ref.
Still pregnant	49	29.2	119	70.8	0.71	0.46 – 1.12
Mode of delivery						
Vaginal Birth	43	64.2	24	35.8	1.00	Ref.
C-section	131	61.5	82	38.5	0.96	0.75 – 1.23
Abortion/ ectopic	21	42.0	29	58.0	0.65	0.39 – 1.11
Onset of labor						
Spontaneous	45	57.7	33	42.3	1.00	Ref.
Induction	19	48.7	20	51.3	0.84	0.61 – 1.17
Elective C-section	99	65.6	52	34.4	1.14	0.86 – 1.50
Access to referral center						
Not scheduled	20	71.4	8	28.6	0.90	0.65 – 1.26
Scheduled	105	78.9	28	21.1	1.00	Ref.
Spontaneous	81	32.8	166	67.2	**0.42**	**0.29 – 0.59**
Other	33	40.2	49	59.8	**0.51**	**0.37 – 0.70**
Delays						
Women/family members	104	54.2	88	45.8	**1.36**	**1.04 – 1.76**
Health service	68	79.1	18	20.9	**1.92**	**1.49 – 2.48**
Health professional	80	76.2	25	23.8	**1.88**	**1.41 – 2.50**
Any delays	162	59.1	112	40.9	**1.93**	**1.36 – 2.74**

SMO = Severe Maternal Outcome (maternal near miss plus maternal death); PLTC = Potentially Life-threatening Condition; PR_{adj} = prevalence ratio adjusted for cluster effect; CI = confidence interval.
Values in bold mean they are statistically significant

Table 5. Estimated risks of severe maternal outcomes (SMO = MNM + MD) among women with severe infection and sepsis during pregnancy or childbirth according to conditions of severity management, management criteria and perinatal results

Variables	SMO		PLTC		PR_{adj}	95% CI
	n	%	n	%		
Conditions of severity management						
Blood transfusion	141	77.5	41	22.5	**2.34**	**1.52 – 3.60**
Central venous access	169	89.9	19	10.1	**3.62**	**2.52 – 5.19**
ICU admission	221	71.3	89	28.7	**5.26**	**2.86 – 9.69**
Hospital stay >7days	194	65.8	101	34.2	**2.57**	**1.84 – 3.58**
Invasive mechanical ventilation	139	97.9	3	2.1	**3.26**	**2.43 – 4.38**
Return to operating room	52	69.3	23	30.7	**1.52**	**1.15 – 2.00**
Hysterectomy/laparotomy	48	81.4	11	18.6	**1.81**	**1.49 – 2.21**
Other surgical procedures	23	74.2	8	25.8	**1.56**	**1.17 – 2.08**
Management criteria						
Use of continuous vasoactive drugs	117	100.0	0	0.0	**2.96**	**2.14 – 4.09**
Hysterectomy following infection/hemorrhage	39	100.0	0	0.0	**2.23**	**1.74 – 2.85**
Transfusion of $\geq$ 5 units red cell transfusion	56	100.0	0	0.0	**2.34**	**1.77 – 3.08**
Intubation and ventilation for $\geq$60 minutes not related to anesthesia	138	100.0	0	0.0	**3.34**	**2.52 – 4.43**
Dialysis for acute renal failure	35	100.0	0	0.0	**2.20**	**1.72 – 2.82**
CPR	54	100.0	0	0.0	**2.32**	**1.81 – 2.98**
Perinatal results						
Apgar at 5 min < 7	45	84.9	8	15.1	**1.66**	**1.31 – 2.10**
Apgar at 5 min $\geq$ 7	86	51.2	82	48.8	1.00	Ref.
Birth weight < 2500g	90	72.0	35	28.0	**1.66**	**1.06 – 2.58**
Birth weight $\geq$ 2500g	43	43.4	56	56.6	1.00	Ref.
Still birth	34	91.9	3	8.1	**1.64**	**1.31 – 2.04**
Live birth	119	56.1	93	43.9	1.00	Ref.
Neonatal death	5	55.6	4	44.4	1.10	0.50 – 2.44
NICU admission*	42	62.7	25	37.3	1.24	1.00 – 1.54
Hospital discharge	59	50.4	58	49.6	1.00	Ref.
Abortion	21	43.8	27	56.2	0.88	0.51 – 1.53

CI = confidence interval; CPR = Cardio pulmonary resuscitation; *NICU = Neonatal Intensive Care Unit; PLTC = Potentially Life-threatening Condition; PR_{adj} = Prevalence Ratio adjusted for cluster effect; SMO = Severe Maternal Outcome (maternal near miss plus maternal death);
Values in bold mean they are statistically significant

Table 6. Variables independently associated with a worse maternal outcomes (MNM + MD) among women with severe infection and sepsis during pregnancy or childbirth (Poisson multiple regression analyses, n = 460)

Variables	PR_{adj}	95% CI	p
Hysterectomy following infection/hemorrhage	1.52	1.29 - 1.80	<0.001
Other major surgical procedures	0.81	0.73 - 0.91	<0.002
Central venous access	1.48	1.20 - 1.83	<0.002
Hospital stay >7days	1.54	1.20 - 1.97	<0.002
Medical history HIV/ Aids	1.49	1.15 - 1.94	0.004
ICU admission	2.62	1.38 - 4.97	0.005
Delay of healthcare system	1.29	1.07 - 1.54	0.008
Intubation and ventilation for ≥60 minutes not related to anesthesia	1.44	1.10 - 1.89	0.010
Use of continuous vasoactive drugs	1.24	1.02 - 1.51	0.032

PR_{adj} = prevalence ratio adjusted for cluster effect and all other predictors; CI = confidence interval.
Multiple Poisson regression, controlled by: Age (years); Marital status (married/with partner: 1; others: 0); Schooling (Up to high school: 0; University: 1); Skin color (white: 0; no white: 1); Number of pregnancies (1:/≥2:1); Previous C-sections (0; ≥1: 1); Parity (0; ≥1: 1); Previous hypertension (yes: 1; no: 0); Previous obesity (yes: 1; no: 0); Previous low weight (yes: 1; no: 0); Previous diabetes (yes: 1; no: 0); Previous smoking (yes: 1; no: 0); Previous cardiac disease (yes: 1; no: 0); Previous respiratory disease (yes: 1; no: 0); Previous renal diseases (yes: 1; no: 0); Previous sickle cell disease or thalassemia (yes: 1; no: 0); Previous HIV/AIDS (yes: 1; no: 0); Previous thyroid diseases (yes: 1; no: 0); Previous neurological diseases (yes: 1; no: 0); Previous collagen diseases (yes: 1; no: 0); Previous neoplasms (yes: 1; no: 0); Previous drug addiction (yes: 1; no: 0); Coverage for prenatal care (public: 0/ other:1); Adequacy of prenatal care (yes: 1; no: 0); Gestational age at admission (<37 or postpartum: 1; ≥37: 0); Gestational age at pregnancy termination (<37: 1; ≥37: 0); Mode of delivery (vaginal: 0/ C-section: 1); Onset of labor (Spontaneous:0 /Other:1); How the woman reached the hospital (planned:0 /Other:1); Delay related to patient or relatives (yes: 1; no: 0); Delay related to heath system or facility (yes: 1; no: 0); Delay related to health professionals (yes: 1; no: 0); Any delay (yes: 1; no: 0); Transfusion of blood derivatives (yes: 1; no: 0); Central venous access (yes: 1; no: 0); Admission to ICU (yes: 1; no: 0); Prolonged hospital stay (yes: 1; no: 0); Intubation not related to anesthesia (yes: 1; no: 0); Returning to operating room (yes: 1; no: 0); hysterectomy/laparotomy (yes: 1; no: 0); Other major surgical procedure (yes: 1; no: 0); Continuous use of vasoactive drug (yes: 1; no: 0); hysterectomy due to infection or hemorrhage (yes: 1; no: 0); transfusion of 5 or more units of red cells (yes: 1; no: 0); intubation and ventilation ≥60 min (yes: 1; no: 0); dialysis for acute renal insufficiency (yes: 1; no: 0); cardio pulmonary resuscitation (yes: 1; no: 0).

4. Discussão Geral

Este estudo utilizou os critérios de *near miss* da OMS em uma amostra grande e representativa das cinco regiões do Brasil para estimar a ocorrência de complicações maternas graves atribuíveis à infecção severa durante a gestação, parto e puerpério. Embora a condição infecciosa seja um evento raro entre os demais casos de morbidade materna grave, apresenta grande impacto em mortalidade, sendo responsável por um quarto do total de NMM e por quase metade dos casos de MM, quando avaliados casos de sepse grave, meningite e A(H1N1)pdm09 e quase dois terços quando avaliada a doença respiratória grave.

Neste sentido, a utilização dos indicadores de saúde é ferramenta útil para a compreensão dos resultados encontrados (37). A relação NMM:MM mostra um risco de morte quase três vezes maior entre os casos de infecção, quando comparado a outras causas de morbidade e uma surpreendente relação de NMM abaixo de uma para cada MM entre os casos de infecção confirmada por doença respiratória associada a A(H1N1)pdm09, evidenciando a gravidade e letalidade da pandemia.

Outro indicador importante a ser considerado é o índice de mortalidade (IM). Este índice fornece uma estimativa do desempenho dos serviços de saúde, onde valores de IM superiores a 20% demonstram que a qualidade dos cuidados prestados a casos graves precisa ser revista (37). Em todas as análises realizadas para os casos de infecção, foi encontrado um IM superior a 20%, chegando a ser superior a 50% dentre os casos de A(H1N1)pdm09, o que reflete o despreparo do sistema de saúde brasileiro para o atendimento dos casos infecção na gravidez e puerpério, pelo menos no momento em que o

estudo foi realizado. Estudos mostram que países de alta renda, em que os serviços de saúde estão preparados para atender casos graves e complexos, podem apresentar índices de mortalidade tão baixos como 2% (38).

Houve também grande associação entre demoras no atendimento e pior desfecho materno para os casos de infecção. Sabe-se que demoras, em qualquer esfera de cuidado, estão associadas a piores resultados maternos (35). Estudo publicado recentemente mostra a relação crescente entre as demoras no atendimento e a evolução para maior gravidade (39).

Sabe-se que as infecções no período gravídico-puerperal tendem a progredir rapidamente para morte materna e merecem atenção especial por parte dos profissionais e sistemas de saúde. Neste sentido, o desenvolvimento de diretrizes específicas para o manejo da sepse na gravidez é uma questão que merece ser considerada, tendo em vista a importância do diagnóstico precoce e tratamento adequado nos casos de sepse. Segundo relatório da OMS, a grande maioria das mortes maternas pode ser evitada com adequada gestão em saúde e cuidados que incluem acesso ao pré-natal, atendimento qualificado durante o parto e o puerpério e manejo adequado e oportuno das complicações (40).

Mesmo em cenários de alta renda, os efeitos de uma epidemia podem ser graves e o controle depende de intervenção rápida e ação global. Os resultados apresentados neste estudo demonstram os efeitos da epidemia e confirmam uma maior gravidade entre os casos de A(H1N1)pdm09 quando comparados a outras doenças respiratórias (41). Entretanto, não foi possível caracterizar de maneira mais detalhada os casos de A(H1N1)pdm09, tendo em vista a falta de dados no estudo original da Rede Brasileira de Vigilância da Morbidade Materna Grave sobre sintomas clínicos de infecção por influenza (febre e tosse), tempo desde início da sintomatologia, resultado de exames laboratoriais ou de imagem. Outra limitação deste estudo foi a incapacidade de caracterizar em detalhes o grupo definido como complicações decorrentes de “insuficiência respiratória aguda”, por falta de informações na ficha de coleta que permitissem precisa avaliação de causa-efeito das complicações

decorrentes de edema pulmonar, pneumonia, asma grave, cardiopatia ou aspiração, que são descritas na literatura como as principais etiologias para este grupo (42).

O uso de diretrizes adequadas, de sensibilização e medidas de prevenção contra a gripe, tem mostrado grande impacto em indivíduos com risco aumentado de desenvolver doença respiratória grave, como é o caso das mulheres grávidas (43-45). Dessa forma, a fim de evitar a evolução para piores desfechos maternos, a vacinação contra o vírus A(H1N1)pdm09 tem sido recomendada durante a gestação e a terapia antiviral empírica iniciada o mais breve possível na suspeita de doença respiratória (23).

A padronização das informações nas instituições de saúde, bem como e o conhecimento do profissional de saúde sobre meios de transmissão, sinais e sintomas e as medidas de prevenção contra o vírus A(H1N1)pdm09, são de extrema importância para a redução da mortalidade. No entanto, observa-se que informações equivocadas são frequentes entre os profissionais de saúde e podem colaborar para o atendimento inadequado de gestantes sob-risco de infecção por influenza (46). Infelizmente o presente estudo não possui registro sobre o uso de terapia antiviral ou vacinação entre os casos de morbidade materna devido à doença respiratória.

Outro aspecto importante é avaliar com critério os resultados e o valor dos testes diagnósticos para influenza A(H1N1)pdm09 durante a pandemia. Certamente mulheres sem teste colhido não podem ser excluídas da análise e ainda para aquelas com teste negativo, seria importante avaliar como, quando e onde foi realizado o exame, para realmente poder excluir complicação por influenza H1N1, especialmente para os resultados colhidos no início da disseminação e pandemia (47,48). Não temos maiores detalhes sobre a coleta dos exames laboratoriais para o presente estudo, no entanto, os resultados mostram maior gravidade entre os casos testados e positivos, mas ainda assim, grande impacto para os casos não testados e testados e negativos, quando comparados com demais causas de morbidade materna.

Embora as mortes maternas por causa obstétrica direta sejam mais prevalentes entre a população, encontramos uma alta ocorrência de infecção grave relacionada ao foco pulmonar. Estudo realizado pela OMS destacou que mulheres com causas indiretas subjacentes tiveram risco sete vezes maior de desenvolverem complicações obstétricas e 28 vezes maior de associação com desfecho materno grave (49). Dentre os caos de sepse grave, a maior prevalência de infecção de foco pulmonar, está certamente relacionada à pandemia pelo vírus A(H1N1)pdm09 ocorrida durante o período do estudo (50). O segundo foco mais frequente foi o uterino, seguido pelo urinário, sendo este último responsável por maior gravidade de doença, em concordância com a literatura (51).

A análise de características sócio-demográficas associadas à maior gravidade não apresentou semelhança com os resultados descritos na literatura atual sobre fatores de risco para o desenvolvimento do sepse grave associada à gestação (52). A ausência de dados estatisticamente significativos associados a resultados maternos mais graves pode ser explicado pelo fato da população do estudo ser composta somente por casos de morbidade grave comparando CPAV e desfecho materno grave. A estratificação utilizada para idade, mostrou menor risco de evolução para gravidade entre 30-39 anos para os casos complicados por A(H1N1)pdm09. Sabe-se que a evolução da infecção é pior nos extremos de idade, pelas especificidades da adolescência e pela maior incidência de comorbidades com o aumento da idade materna (34).

A avaliação da idade gestacional no parto mostrou que, entre 22 e 36 semanas de gestação, as mulheres com morbidade grave e infecção apresentam maior risco para pior evolução, entretanto devido ao desenho deste estudo, não é possível afirmar se a prematuridade seja causa ou consequência de uma complicação infecciosa grave. Para a avaliação de complicações por influenza A(H1N1)pdm09, o número de casos não permitiu maior estratificação. Sabe-se que existem limitações ao se avaliar um subgrupo contemplando casos entre 22-36 semanas, uma vez que a evolução materna e perinatal é muito diferente comparando segundo e terceiro trimestres. A abordagem diante de um

caso grave de A(H1N1)pdm09 também é absolutamente diferente, inclusive quanto á discussão de resolução, quando existe viabilidade fetal (especialmente após 28 semanas).

A prematuridade é uma das principais preocupações quando se considera a saúde materna (53). Estudo sobre parto prematuro terapêutico no Brasil aponta para a presença de complicação materna em mais de 70% das resoluções da gravidez antes do termo (54). As características da gravidez e resultados perinatais de acordo com causa de morbidade demonstraram que gestações complicadas por doenças respiratórias têm maior risco de parto prematuro e resultados perinatais piores, sendo concordante com achados descritos anteriormente (23,55). Estudos têm mostrado que a vacinação durante o primeiro trimestre pode melhorar esses desfechos e reduzir as taxas de natimortalidade, sem aumento no risco de malformações (56).

A avaliação da história clínica indica que a presença de diabetes foi associada a maior risco de gravidade em casos de doença respiratória, o que foi claramente demonstrado em estudos anteriores, sendo um dos principais fatores de risco para a morte de A(H1N1)pdm09 (56). O abuso de drogas também foi associado ao aumento do risco de desfecho materno grave entre os casos complicados por doença respiratória, o que corrobora com relatos prévios existentes na literatura (57,58).

A análise multivariada identificou fatores associados de forma independente com desfecho materno grave em mulheres com a infecção severa, como: histerectomia, hospitalização prolongada e antecedente de infecção por HIV, em concordância com estudos prévios sobre sepse materna (15,18). Como esperado, para os critérios de manejo de gravidade, as intervenções foram mais relacionadas com o aumento da gravidade. Entretanto, a coleta transversal dos dados deste estudo não nos permite inferir uma relação de causa e efeito para a prevalência de procedimentos usados para manejo de gravidade, bem como os critérios de manejo de *near miss*, embora a literatura já tenha comprovado que alguns destes procedimentos sejam fatores de risco para desenvolvimento de infecção (12,16). O único fator de proteção

encontrado foi "outros grandes procedimentos cirúrgicos", o que representou principalmente, na amostra estudada, drenagem de abscesso. Especialmente depois de complicações devidas a um procedimento cirúrgico (como cesariana, que foi bastante elevada neste estudo) esta intervenção é a que pode ter um efeito no controle da infecção (59).

Para este estudo, considerou-se que a melhor abordagem para compreender o papel da infecção na Rede Brasileira de Vigilância de Morbidade Materna Grave seria incluir casos complicados não somente por sepse grave, mas também por meningite e suspeita ou confirmação de A(H1N1)pdm09. Embora seja uma complicação grave, meningite na gestação é um evento raro e, neste estudo, contribuiu com apenas dois casos.

Na literatura, existem apenas relatos de casos de meningite em gestantes, com grande morbidade e mortalidade materna e perinatal, especialmente nos casos de doença bacteriana (60). Meningite bacteriana aguda chega a ter taxa de mortalidade superior a 20% em adultos (61), com evolução rápida e, muitas vezes, presença de sinais e sintomas não-específicos, ainda mais durante a gestação.

Esta abordagem mais ampla da infecção na Rede Brasileira de Vigilância de Morbidade Materna Grave dificultou a comparação com dados de existentes na literatura. Contudo, este estudo apresentou resultados de morbidade materna grave, segundo as atuais definições da OMS, em um país de média renda, considerando as complicações durante todo o período gestacional e puerpério em uma coleta prospectiva de dados.

Compreender o impacto da morbidade e mortalidade materna por causa infecciosa, no Brasil e no mundo, pode gerar medidas capazes de colaborar para a melhoria do cuidado obstétrico e redução da mortalidade. Informar as autoridades sobre esta questão e investir em intervenções específicas para gravidez, visando diagnóstico precoce e tratamento oportuno, pode colaborar para melhor assistência durante a gestação e pós-parto.

5. Conclusões

- A morbidade materna grave por infecção foi um evento raro, no entanto apresentou grande impacto sobre o número de desfechos maternos graves, sendo responsável por quase ¼ de todos os casos de NMM e quase metade dos casos de MM. Os indicadores de saúde avaliados demonstram a maior gravidade dos casos complicados por infecção, com índice de mortalidade superior a 26% em comparação com 11% para as demais causas de morbidade grave. Condição médica pré-existente de diabetes, câncer, abuso de drogas e baixo peso, além de prematuridade e demoras no atendimento, monstraram associação com evolução para pior prognóstico (NMM e MM).

- As doenças respiratórias graves na gravidez, parto e puerpério foram associadas a elevadas taxas de *near miss* e morte materna, sendo a infecção por A(H1N1)pdm09 responsável por maior letalidade. A presença de comorbidades, como diabetes e abuso de drogas, foi

associada a aumento do risco de desfecho materno grave na vigência de doença respiratória na gestação ou puerpério. Gestações complicadas por doenças respiratórias apresentaram associação com parto pré-termo e resultados perinatais desfavoráveis.

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7. Anexos

7.1. Anexo 1 – Parecer do CEP

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

www.fcm.unicamp.br/pesquisa/etica/index.html

CEP, 05/03/09.
(Grupo III)

PARECER CEP: Nº 097/2009 (Este nº deve ser citado nas correspondências referente a este projeto)
CAAE: 0071.1.146.000-09

I - IDENTIFICAÇÃO:

PROJETO: **"REDE NACIONAL DE VIGILÂNCIA DA MORBIDADE MATERNA GRAVE: A GRAVIDEZ NA ADOLESCÊNCIAE O ABORTO COMO FATORES DE AGRAVO À SAÚDE".**
PESQUISADOR RESPONSÁVEL: José Guilherme Cecatti.
INSTITUIÇÃO: CAISM/UNICAMP
APRESENTAÇÃO AO CEP: 06/02/2009
APRESENTAR RELATÓRIO EM: 05/03/10 (O formulário encontra-se no *site* acima)

II - OBJETIVOS

Desenvolver uma rede nacional de cooperação científica para vigilância da morbidade materna grave, com ênfase na adolescência e aborto.

III - SUMÁRIO

Estudo de corte transversal multicêntrico, a ser implementado com 25 unidades obstétricas de referência nas diversas regiões geográficas do Brasil. Durante um período de doze meses, os pesquisadores principais e os pesquisadores locais deverão realizar vigilância prospectiva de todas as mulheres internadas nessas unidades, para a identificação dos casos de near miss materno e morbidade materna grave não-near miss. Foi realizado cálculo do tamanho amostral, estimando-se que será necessária a vigilância de um total aproximado de 75.000 partos. Os dados serão coletados em ficha específica e enviados ao banco de dados central através de formulário eletrônico disponível no website do projeto. Análise de dados: A análise dos dados será feita por sub-grupos de acordo com a época da ocorrência do near miss ou morbidade materna grave (na adolescência e em outros momentos de sua vida reprodutiva) e causa determinante (aborto e outras causas), estimando-se as respectivas taxas, razões e riscos relativos para os respectivos preditores.

IV - COMENTÁRIOS DOS RELATORES

Após respostas às pendências, o projeto encontra-se adequadamente redigido e de acordo com a Resolução CNS/MS 196/96 e suas complementares, bem como a dispensa do Termo de Consentimento Livre e Esclarecido.

V - PARECER DO CEP

Comitê de Ética em Pesquisa - UNICAMP
Rua: Tessália Vieira de Camargo, 126
Caixa Postal 6111
13083-887 Campinas – SP

FONE (019) 3521-8936
FAX (019) 3521-7187
cep@fcm.unicamp.br

O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP, após acatar os pareceres dos membros-relatores previamente designados para o presente caso e atendendo todos os dispositivos das Resoluções 196/96 e complementares, resolve aprovar sem restrições o Protocolo de Pesquisa, bem como ter aprovado a dispensa do Termo do Consentimento Livre e Esclarecido, assim como todos os anexos incluídos na Pesquisa supracitada.

O conteúdo e as conclusões aqui apresentados são de responsabilidade exclusiva do CEP/FCM/UNICAMP e não representam a opinião da Universidade Estadual de Campinas nem a comprometem.

VI - INFORMAÇÕES COMPLEMENTARES

O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

Pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.1.z), exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade do regime oferecido a um dos grupos de pesquisa (Item V.3.).

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4.). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projeto do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, Item III.2.e)

Relatórios parciais e final devem ser apresentados ao CEP, de acordo com os prazos estabelecidos na Resolução CNS-MS 196/96.

VI I- DATA DA REUNIÃO

Homologado na II Reunião Ordinária do CEP/FCM, em 17 de fevereiro de 2009.

Profa. Dra. Carmen Silvia Bertuzzo
PRESIDENTE DO COMITÊ DE ÉTICA EM PESQUISA
FCM/UNICAMP

Comitê de Ética em Pesquisa - UNICAMP
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7.2. Anexo 2 – Ficha de Coleta Manual de dados da RBVMMG

Rede Nacional de Vigilância de Morbidade Materna Grave - FORMULÁRIO DE COLETA MANUAL

IDENTIFICAÇÃO

1. Centro do Estudo*: ☐☐
2. Subject ID*: _____
3. Person ID*: _____

Data de nascimento*: ☐☐ ☐☐ ☐☐

DADOS PESSOAIS

4. Idade em anos completos*: ☐☐
5. Cor: [ ] 1 negra [ ] 2 branca [ ] 3 indígena [ ] 4 amarela [ ] 5 outro [ ] 8 não consta
6. Escolaridade: [ ] 1 analfabeta [ ] 2 Fundamental incompleto [ ] 3 Fundamental [ ] 4 Médio incompleto [ ] 5 Médio [ ] 6 Superior incompleto [ ] 7 Superior [ ] 8 não consta
7. Estado civil: [ ] 1 casada/amasiada [ ] 2 solteira [ ] 3 separada/divorciada [ ] 4 viúva [ ] 8 não consta
8. Peso em kg: _____
9. Altura em m: _____
10. Data da internação no centro*: ☐☐ ☐☐ ☐☐
11. A paciente fazia pré-natal no serviço?* [ ] 1 sim [ ] 2 não [ ] 3 sem pré-natal [ ] 8 não consta
12. Como foi o acesso da mulher ao centro?* [ ] 1 procura espontânea [ ] 6 encaminhamento da própria instituição [ ] 2 transferência por serviço de resgate/emergência [ ] 8 não consta [ ] 3 transferência inter hospitalar programada [ ] 4 transferência inter hospitalar não programada [ ] 5 encaminhamento de outro serviço
13. Qual cobertura financeira majoritária do pré-natal? [ ] 1 público [ ] 2 privado [ ] 3 seguro saúde/convênio [ ] 4 sem pré-natal [ ] 8 não consta
14. Qual cobertura financeira majoritária da internação?* [ ] 1 público [ ] 2 privado [ ] 3 seguro saúde/convênio [ ] 8 não consta

DADOS OBSTÉTRICOS

15. Número de gestações*: ☐☐
16. Número de partos*: ☐☐
17. Número de abortos*: ☐☐
18. Número de cesáreas prévias*: ☐☐
19. Número de nascidos vivos*: ☐☐
20. Anos desde o último parto: ☐☐
21. A mulher possui cirurgia uterina prévia? (excluindo cesárea seg. transv) [ ] 1 sim [ ] 2 não [ ] 8 não consta
22. Número de consultas de pré-natal*: ☐☐
23. A mulher estava grávida quando foi admitida?* [ ] 1 sim [ ] 2 não [ ] 8 não consta
24. Idade gestacional na internação*: ☐☐
25. Forma de início do trabalho de parto*: [ ] 1 espontâneo [ ] 2 induzido [ ] 3 sem trabalho de parto [ ] 4 aborto [ ] 5 continua grávida [ ] 8 não consta
26. Data da resolução da gestação: ☐☐ ☐☐ ☐☐
27. Idade gestacional na resolução*: ☐☐
28. Como foi ultimada a gestação? [ ] 1 parto vaginal [ ] 5 aborto [ ] 2 parto vaginal operatório [ ] 6 prenhez ectópica [ ] 3 parto cesárea antes do início do trabalho de parto [ ] 7 continua grávida [ ] 4 parto cesárea após o início do trabalho de parto [ ] 8 não consta

ABORTO

29. Como se iniciou o aborto? [ ] 1 espontâneo [ ] 2 induzido [ ] 8 não consta
30. O aborto foi mais provavelmente seguro ou inseguro? [ ] 1 seguro [ ] 2 inseguro [ ] 8 não consta
31. Quais procedimentos foram realizados? [ ] 1 dilatação e/ou curetagem [ ] 2 ocitocina [ ] 3 vácuo aspiração [ ] 4 prostaglandinas [ ] 5 outros [ ] 6 nenhum [ ] 8 não consta
32. Se outro procedimento, especifique: _____

DADOS DO RN

33. Número total de nascidos: ☐☐
34. Qual era a apresentação fetal ao nascimento? [ ] 1 cefálico [ ] 2 pélvico [ ] 3 outro [ ] 8 não consta
35. Sexo: [ ] 1 feminino [ ] 2 masculino [ ] 3 indeterminado [ ] 8 não consta
36. Condição do nascimento: [ ] 1 vivo [ ] 3 natimorto anteparto [ ] 2 natimorto intra-parto [ ] 8 não consta
37. Qual foi o Apgar de 1º. Minuto? ☐☐
38. Qual foi o Apgar de 5º. Minuto? ☐☐
39. Peso em gramas: ☐☐☐☐
40. Desfecho neonatal: [ ] 1 alta [ ] 2 internado [ ] 3 óbito neonatal precoce (<7dias) [ ] 4 óbito neonatal tardio (8-28 dias) [ ] 5 transferido [ ] 8 não consta
41. Se gemelar, informe os dados dos outros RN: _____ _____

CONDIÇÕES MATERNAS PRÉ-EXISTENTES

42. A mulher apresentava alguma condição patológica/ de risco prévios à gestação?* [ ] 1 sim [ ] 2 não [ ] 8 não consta
43. Quais condições estavam presentes? [ ] 1 hipertensão arterial crônica [ ] 9 anemia falciforme-talassemia [ ] 2 obesidade [ ] 10 HIV/AIDS [ ] 3 baixo peso [ ] 11 tireoidopatias [ ] 4 diabetes mellitus [ ] 12 doenças neurológicas / epilepsia [ ] 5 tabagismo [ ] 13 colagenoses [ ] 6 doenças cardíacas [ ] 14 neoplasias [ ] 7 doenças respiratórias [ ] 15 outro [ ] 8 doenças renais [ ] 16 drogadição
44. Se outra condição patológica, especifique: _____

CONDIÇÕES POTENCIALMENTE AMEAÇADORAS DA VIDA

45. Houve alguma complicação hemorrágica?* [ ] 1 sim [ ] 2 não [ ] 8 não consta
46. Qual complicação hemorrágica ocorreu no período?* [ ] 1 descolamento prematuro de placenta [ ] 5 hemorragia grave por aborto [ ] 2 placenta prévia/acreta/increta/percreta [ ] 6 hemorragia pós parto [ ] 3 prenhez ectópica complicada [ ] 7 outra hemorragia grave [ ] 4 rotura uterina [ ] 8 não houve/não consta
47. Se HEMORRAGIA PÓS- PARTO, especifique: [ ] 1 atonia [ ] 2 retenção placentária [ ] 3 lacerações de trajeto [ ] 4 coagulopatia [ ] 5 inversão uterina [ ] 6 outra causa obstétrica

48. Houve alguma complicação hipertensiva?*[ ] 1 sim [ ] 2 não [ ] 8 não consta

49. Qual complicação hipertensiva ocorreu no período?*

[ ] 1 pré-eclâmpsia grave [ ] 2 eclâmpsia [ ] 3 hipertensão grave
[ ] 4 HELLP síndrome [ ] 5 fígado gorduroso [ ] 8 não houve / não consta

50. Houve alguma outra complicação?*[ ] 1 sim [ ] 2 não [ ] 8 não consta

51. Quais complicações?*

[ ] 1 edema pulmonar [ ] 2 convulsões [ ] 3 trombocitopenia < 100 mil
[ ] 4 crise tireotoxica [ ] 5 choque [ ] 6 insuf. respiratória aguda
[ ] 7 acidose [ ] 8 cardiopatia [ ] 9 AVC
[ ] 10 dist. de coagulação [ ] 11 CIVD [ ] 12 tromboembolismo
[ ] 13 cetoacidose diabética [ ] 14 icterícia/disf hepática [ ] 15 meningite
[ ] 16 sepse grave [ ] 17 IRA [ ] 88 não houve / não consta
[ ] 18 complicação associada à suspeita ou confirmação de Influenza A (H1N1)

52. Se SEPSE GRAVE, especifique o foco:

[ ] 1 endometrite pós-parto [ ] 2 endometrite pós aborto [ ] 3 foco pulmonar
[ ] 4 foco urinário [ ] 5 outro [ ] 8 não consta [ ] 9 ignorado

53. Se outro foco, especifique:_____

54. A mulher apresentou alguma das condições de manejo de gravidade?*

[ ] 1 sim [ ] 2 não [ ] 8 não consta

55. Quais condições estavam presentes?*

[ ] 1 transfusão de hemoderivados [ ] 6 retorno à sala cirúrgica
[ ] 2 acesso venoso central [ ] 7 histerectomia/laparotomia
[ ] 3 admissão em UTI [ ] 8 uso de sulfato de magnésio
[ ] 4 hospitalização prolongada (>7 dias) [ ] 9 outro proc. cirúrgico maior
[ ] 5 intubação não relacionada à anestesia [ ] 88 não houve/não consta

CRITÉRIOS DE NEAR MISS MATERNO

56. A mulher apresentou algum dos critérios clínicos de near miss?*

[ ] 1 sim [ ] 2 não [ ] 8 não consta

57. Se SIM, indique quais*:

[ ] 1 cianose [ ] 9 acidente vascular cerebral
[ ] 2 gasping [ ] 10 convulsão não controlada – paralisia total
[ ] 3 FR > 40 ou < 6 [ ] 11 icterícia na presença de pré-eclâmpsia
[ ] 4 choque [ ] 88 não houve / não consta
[ ] 5 oligúria não responsiva a fluidos ou diuréticos
[ ] 6 distúrbios de coagulação
[ ] 7 perda da consciência durante 12 h ou mais
[ ] 8 ausência de consciência E ausência de pulso-batimento cardíaco

58. A mulher apresentou algum dos critérios laboratoriais de near miss?*

[ ] 1 sim [ ] 2 não [ ] 8 não consta

59. Se SIM, indique quais*:

[ ] 1 saturação de O_2 < 90% por > 60 min.
[ ] 2 PaO_2/FiO_2 < 200
[ ] 3 creatinina ≥300mmol/l ou ≥ 3,5 mg/dl
[ ] 4 bilirrubina ≥ 100 mmol/l ou ≥ 6 mg/dl
[ ] 5 pH < 7,1
[ ] 6 lactato > 5
[ ] 7 plaquetas < 50 mil
[ ] 8 ausência de consciência e presença de glicose e cetoácidos na urina
[ ] 88 não houve / não consta

60. A mulher apresentou algum dos critérios de manejo?*

[ ] 1 sim [ ] 2 não [ ] 8 não consta

61. Se SIM, indique quais*:

[ ] 1 uso de droga vasoativa contínua [ ] 6 R. Cardiopulm. (RCP)
[ ] 2 histerectomia por infecção ou hemorragia [ ] 88 não houve / não consta
[ ] 3 transfusão de ≥ 5 U de hemácias
[ ] 4 intubação e ventilação por ≥ 60 minutos não relacionada com anestesia
[ ] 5 diálise para insuficiência renal aguda

62. Alguma dessas condições já estava presente na admissão do sujeito?

[ ] 1 sim [ ] 2 não [ ] 3 não se aplica [ ] 8 não consta

DESFECHO MATERNO

63. Data da alta, transferência ou óbito*: ☐☐ ☐☐ ☐☐

64. Qual foi a condição de alta da mulher?*

[ ] 1 alta médica [ ] 2 alta a pedido [ ] 3 transferência [ ] 4 óbito [ ] 5 evasão

65. Comentários ou observações referentes a dados incluídos e dados relativos à transferência do sujeito: _____

_____

PESQUISA DE DEMORAS NO ATENDIMENTO

66. Durante o atendimento do caso, houve alguma demora relacionada ao serviço e/ou sistema de saúde?* [ ] 1 sim [ ] 2 não [ ] 9 ignorado

Se houve demora, especifique: (se NÃO houve, deixe em branco)

1 nível primário 2 nível secundário 3 nível terciário

67. Falta de medicação (sulfato, ATB, DVA, uterotônicos): ☐
68. Dificuldade ou problemas com transporte municipal / hospitalar): ☐
69. Dificuldade na comunicação (hospitalar/central reguladora): ☐
70. Ausência de hemoderivados: ☐
71. Dificuldade para monitorização (unidade de cuidados intensivos): ☐
72. Falta de pessoal treinado: ☐
73. Dificuldade de acesso ao pré-natal: ☐

74. Houve alguma demora relacionada ao paciente e/ou seus familiares?*

[ ] 1 sim [ ] 2 não [ ] 9 ignorado

75. Se resposta SIM, especifique quais:

[ ] 1 demora na procura ao Serv. Saúde
[ ] 2 dificuldade geográfica ao acesso ao Serv. Saúde
[ ] 3 recusa ao tratamento
[ ] 4 Pré-natal ausente ou inadequado
[ ] 5 Aborto inseguro

76. Houve alguma demora na assistência relacionada aos profissionais de saúde?* [ ] 1 sim [ ] 2 não [ ] 9 ignorado

Se houve demora, especifique: (se NÃO houve, deixe em branco)

1 nível primário 2 nível secundário 3 nível terciário

77. Demora no diagnóstico: ☐
78. Demora no início do tratamento: ☐
79. Manejo inadequado do caso: ☐
80. Demora na referência ou transferência do caso: ☐

7.3. Anexo 3 – Artigo do projeto da RBVMMG

Reproductive Health

BioMed Cent

Study protocol

Open Acce

Brazilian network for the surveillance of maternal potentially life threatening morbidity and maternal near-miss and a multidimensional evaluation of their long term consequences

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Abstract

Background: It has been suggested that the study of women who survive life-threatening complications related to pregnancy (maternal near-miss cases) may represent a practical alternative to surveillance of maternal morbidity/mortality since the number of cases is higher and the woman herself is able to provide information on the difficulties she faced and the long-term repercussions of the event. These repercussions, which may include sexual dysfunction, postpartum depression and posttraumatic stress disorder, may persist for prolonged periods of time, affecting women's quality of life and resulting in adverse effects to them and their babies.

Objective: The aims of the present study are to create a nationwide network of scientific cooperation to carry out surveillance and estimate the frequency of maternal near-miss cases, to perform a multicenter investigation into the quality of care for women with severe complications of pregnancy, and to carry out a multidimensional evaluation of these women up to six months.

Methods/Design: This project has two components: a multicenter, cross-sectional study to be implemented in 27 referral obstetric units in different geographical regions of Brazil, and a concurrent cohort study of multidimensional analysis. Over 12 months, investigators will perform

prospective surveillance to identify all maternal complications. The population of the cross-sectional component will consist of all women surviving potentially life-threatening conditions (severe maternal complications) or life-threatening conditions (the maternal near miss criteria) and maternal deaths according to the new WHO definition and criteria. Data analysis will be performed in case subgroups according to the moment of occurrence and determining cause. Frequencies of near-miss and other severe maternal morbidity and the association between organ dysfunction and maternal death will be estimated. A proportion of cases identified in the cross-sectional study will comprise the cohort of women for the multidimensional analysis. Various aspects of the lives of women surviving severe maternal complications will be evaluated 3 and 6 months after the event and compared to a group of women who suffered no severe complications in pregnancy. Previously validated questionnaires will be used in the interviews to assess reproductive function, posttraumatic stress, functional capacity, quality of life, sexual function, postpartum depression and infant development.

Background

Currently, more than half a million maternal deaths occur annually worldwide. Although an extremely rare event in developed countries, maternal mortality is higher in less developed countries. Better social conditions, better medical care in cases of severe complication and family planning are factors that contribute to reducing maternal mortality [1].

Nevertheless, quantifying maternal mortality in Brazil is a complex task. The Ministry of Health estimates the maternal death ratio at 75 maternal deaths per 100,000 live-born infants [2]. Reflecting the complexity of this estimate, other agencies, using different methods, have calculated maternal death ratios twice or even four times higher than the official figures [3,4].

Notwithstanding, the recorded cases of maternal deaths constitute a tiny proportion of the whole problem. Around the world, millions of women present severe maternal complications every year and the precise size of this specific population currently remains unknown. For this reason, women who have survived severe complications of pregnancy have in recent years sparked the attention of investigators and healthcare administrators. The World Health Organization (WHO) developed the maternal near-miss approach, a tool to uniformly identify near-miss cases and evaluate quality of care provided to women presenting severe complications. WHO defines a maternal near miss case as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy [5].

Therefore, the study of maternal near-miss cases has been suggested as a practical alternative to the surveillance of maternal morbidity and mortality, mainly in view of the larger number of cases and because the woman herself is able to provide information on the event and on the difficulties she had to face. It is believed that auditing near-miss cases would enable even smaller services to evaluate how the determinants of severe maternal morbidity (and consequently the determinants of maternal death) affect their users and services [6,7].

In addition, little is known on the long-term repercussions of severe, life-threatening complications related to pregnancy. An acute stress disorder associated with the occurrence of severe maternal complications has been suggested, but further research is needed. [8]. The repercussions of these events may lead to adverse effects in the women and their children, may negatively affect their quality of life and may persist for extended periods of time after the event [9-12].

Among the possible repercussions, studies have been carried out to evaluate the psychological impact and occurrence of posttraumatic stress disorder (PTSD), postpartum depression and changes in sexual health following delivery [10,13-17]. Considering that other factors such as mode of delivery, medical interventions and obstetrical complications [9,18,19] negatively affect women's quality of life, it is probable that in dramatic situations such as near-misses such repercussions would be even more evident. According to some authors, evaluation of the state of health, quality of life and sexual function of patients who suffered severe complications is poorer in the immediate postpartum period [15,20-23].

Nevertheless, doubts remain with respect to the long-term health status of women who suffer severe acute maternal morbidity and near-miss. Investigation of various aspects related to mental health and quality of life may offer a valuable perspective on the effect of maternal morbidity on the life of these women.

Studying the occurrence of severe complications in pregnancy and the factors associated with this event will result in a greater understanding of the process that occurs in

these women taking them from a state of health to one of sickness. Further knowledge on this issue may collaborate towards improving public policies and the healthcare provided to women who develop severe acute maternal morbidity.

Therefore, the objective of the present project is to evaluate this issue using clear goals to differentiate it from previous studies. These goals include estimating the frequency of the occurrence of maternal near-miss using a uniform set of criteria, carrying out a multicenter investigation into the quality of care provided to women with severe complications of pregnancy and performing a longitudinal evaluation of the quality of life of these women following the event.

Objectives and Hypothesis

The overall objective is to develop a nationwide network of scientific cooperation for the surveillance of severe maternal complications and maternal near-miss and their consequences.

Specific objectives

- To determine the frequency of maternal near-miss in healthcare facilities of different levels of complexity situated in different regions of Brazil, using the World Health Organization (WHO)'s new set of criteria for near-miss [5];
- To determine the frequency of non-near-miss severe maternal morbidity in these facilities using specifically defined potentially life threatening conditions;
- To evaluate the association between the indicators of organ dysfunction used to define maternal near-miss and the risk of maternal death;
- To determine the frequency of near-miss and non-near-miss severe maternal morbidity according to age-group and specific causes;
- To examine the occurrence of avoidable factors and other factors associated with maternal near-miss;
- To investigate the repercussions of severe maternal morbidity and near-miss on the quality of life of survivors up to six months after the event;
- To investigate the presence of sexual dysfunction, posttraumatic stress disorder and postpartum depression, as well as women's perception of their functional status in routine activities in the six months following an occurrence of severe maternal morbidity.
- To investigate the immediate perinatal outcome and subsequent neuromotor and weight-height development in children born from pregnancies associated with severe maternal morbidity.

Main hypotheses

In survivors of severe acute maternal morbidity:

- health and quality of life would be poorer;
- posttraumatic stress would be more common;
- postpartum depression would be more common;
- sexual function would have deteriorated and the woman's return to sexual activity would take longer;
- functional status in routine activities would be evaluated as poorer.

In the children born from a pregnancy associated with severe maternal morbidity:

- immediate perinatal outcome would be poorer;
- the occurrence of impaired neuromotor and weight-height development would be significantly higher.

Methods/Design

This study has two components: a multicenter cross-sectional study and a concurrent cohort study.

The cross-sectional study will be implemented in 27 referral obstetric units in different geographical regions of Brazil, which have already joined the initiative for building a national network for studies on maternal and reproductive health. Over a 12-month period, the principal and local investigators will carry out prospective surveillance and will collect data for the identification of maternal near-miss and non-near-miss cases, severe maternal morbidity (potentially life threatening conditions) and maternal deaths. To determine the number of collaborating centers to be included in the present study, calculation of sample size took into consideration the number of deliveries that would have to be monitored to identify cases of near-miss and maternal deaths. Previous studies have estimated a maternal near miss incidence of approximately 8 cases per 1000 deliveries [24] and a Brazilian maternal mortality ratio of 140 per 100,000 LB. Therefore, a total of approximately 75,000 deliveries would have to be monitored in order to identify around 100 maternal deaths and 600 maternal near miss cases. These numbers are believed to be sufficient to evaluate the use of the new criteria for near-miss established by the World Health Organization

in 2009 [5] and to perform analysis allowing for level of complexity of health facility, age group and specific cause.

The study population will consist of all the women admitted to the participating hospitals during the study period in whom organ dysfunction is registered (maternal near-miss, Appendix 1), in whom one of the diagnoses defined as non-near-miss severe maternal morbidity is present (Appendix 2), and those who died or were transferred to another healthcare service because of their bad health condition.

For the multidimensional analysis of the repercussions of severe maternal morbidity, a concurrent cohort, specific population study will be carried out with an externally selected comparison group. The main exposure factor will be the occurrence of severe maternal morbidity (both maternal potentially life threatening or near miss conditions). During the second half of the cross-sectional study, a sample of women identified as having severe maternal morbidity will be selected and invited to participate in the longitudinal evaluation. There will be a comparison group composed of women who did not suffer severe maternal morbidity. These women will be randomly selected externally in a proportion of 1:1 from postpartum women in the rooming-in wards of the same maternity hospitals as the cases. Controls will be selected at random and balanced according to mode of delivery, maternal age and gestational age at the time of delivery.

Main outcomes

Maternal near-miss

A woman who fulfills one of the clinical, laboratory or management criteria representing severity as defined by WHO [5] and who survives a complication occurring during pregnancy, childbirth or within 42 days postpartum.

Maternal potentially life threatening condition

A condition of severe morbidity found in women during pregnancy, childbirth or in the puerperium, classified as potentially life threatening conditions [5], including hemorrhagic or hypertensive disorders, other systemic disorders, and indicators of severe management (Appendix 2).

Main cause of complication/death

classification of the determinant main cause of the complication identified among cases and/or the main cause of death.

Maternal death

Death of a woman during pregnancy or within a 42-day period following the end of pregnancy irrespective of the duration or localization of the pregnancy, resulting from any cause related to or aggravated by the pregnancy or by measures taken with respect to it; however, not from accidental or incidental causes.

Conditions at birth

Vital status of the newborn infant as recorded on the medical chart, dichotomized into live or intrauterine death.

Vitality of the newborn infant

Evaluation of the newborn infant according to 1st and 5th minute Apgar scores as shown on the medical chart, classified from 0 to 10.

Neonatal outcome

Condition of the newborn infant at the time of data collection, identified from a review of the medical charts and classified as: discharged from hospital together with the mother, early neonatal death (<7 days) or late neonatal death (7-28 days).

Quality of life

The woman's perception of her position in life within the cultural context and value system in which she lives and in relation to her goals, expectations, health, standards and concerns (WHO); identified by the investigators using a standard SF-36 form.

Posttraumatic stress

Symptoms of intrusion, avoidance and hyperarousal following the occurrence of a pregnancy with severe complications; identified by the investigator using a standard questionnaire (PTSD - Checklist CV).

Ideal number of children

Number of children that the woman considered ideal prior to and following the index pregnancy.

Return to sexual activity

Time taken by the woman to recommence sexual activity after delivery and reason given for not recommencing sexual activity.

Sexual function

Sexual function and response; identified by the investigator using a standard questionnaire (*Female Sexual Function Index - FSFI*).

Postpartum depression

Depressive symptoms following the occurrence of a pregnancy with severe complications; identified by the investigator using a standard questionnaire (Edinburgh Postnatal Depression Scale - EPDS).

Functional status

Perception of the woman with respect to her functional status in six items related to her routine activities (understanding and communicating, getting around, self-care, getting along with people, life activities in the home/at work and participation in society), classified from 0 to 100 (from best to worst) [25].

Neuromotor development in the child born from the index pregnancy
Process of changes in motor behavior that involve both maturation of the central nervous system and interaction with the environment and stimuli given during the child's development; identified by the investigator using the Denver II - Revised Denver Developmental Screening Test [26].

Weight-height development of the child born from the index pregnancy
Process of weight and height increment during the child's development, weight measured in grams and height in centimeters, using scales and anthropometer, classified as adequate or inadequate for age, according to the standards of the World Health Organization [27].

Control variables
maternal age, marital status, place of residence, number of previous pregnancies, parity, previous abortions, previous Cesarean sections, number of children, mode of delivery, gestational age, birthweight, gender of neonate, condition of neonate at discharge, condition of mother at discharge.

Data Collection and Procedures

Cross-sectional component
Research assistants, referred to as local coordinators, will review the charts of hospitalized patients on a daily basis in search of cases with one of the conditions identifying severity (Appendix 2). In cases found with these diagnoses, the relevant hospital records will be reviewed for data collection following the women's hospital discharge, death or transfer to another healthcare facility. Data unavailable on the chart but of interest to the study will be obtained from the attending medical team. For each case included, data will be collected on the demographic and obstetric characteristics of the patient, the primary determinant of maternal near-miss (the first complication to occur in the chain of events leading to severe maternal morbidity), the duration of hospitalization (prior to delivery, following delivery and total time), the occurrence of indicators of maternal near-miss at any time during hospitalization, indicators of perinatal outcome and conditions of the woman at discharge from hospital.

These data will be collected on a previously coded form developed specifically for this purpose. A central database will be constructed and the data will be included by the local investigators themselves using electronic forms. The manually completed forms will be filed and made available at technical visits for the purpose of quality control.

For the electronic inclusion of data, each center will have its own restricted area on the study website where password-protected access will be granted only to cases included at that center. An overview of all the cases included in the network will be provided in the form of monthly graphs and tables containing the number of cases included by each center. In addition, the reported diagnoses will be provided by the coordinating center on the main page of the website.

In cases of near-miss, data will be collected on avoidable factors responsible for their occurrence (delays). These factors will be classified into those related to infrastructure, the patient or the healthcare professionals. Avoidable factors related to infrastructure include cases in which difficulties in obtaining supplies or medication, transportation, communication, blood components or monitoring and treatment may have led to less than ideal care. Factors related to the patient include those generated by the patient herself or her family, either by delaying seeking professional care or by refusing treatment. Factors related to the healthcare team include delays in defining the correct diagnosis and/or inappropriate management.

The degree of complexity at each hospital will be evaluated using an adapted version of the hospital complexity index developed for the WHO Global Survey project [28]. Participating institutions will provide information on a monthly basis via the website on the total number of deliveries, live births and maternal deaths that occurred the previous month. These data will be confirmed by the principal local investigator after data collection is finished.

To minimize the number of uncertainties that research assistants may face during data collection, a manual of operation was produced containing all the necessary information on how to use the internet, how to complete the written and electronic forms and how to access the database of each individual center, as well as information regarding the standardization of diagnostic definitions.

A meeting will be held with the investigators and local coordinators of each center (two individuals from each center) at the study coordinating center immediately preceding initiation of data collection in order to provide adequate training and clarify any queries regarding the data collection process and use of the website. Sometime after the initiation of data collection, a meeting of the study's Steering Committee will also be held. A second meeting will take place involving only the local investigators after data collection has finished to discuss facts related to the previous process, disclosure of partial results, scheduling of the preliminary and final analyses, agreement on papers to be written on the results and assignment of responsibility regarding execution of each item in this process.

Longitudinal component

As in the cross-sectional component, women with one of the conditions indicative of severity will be selected as potential subjects for longitudinal evaluation. Once identified, research assistants who are not involved in the cross-sectional portion of the study will invite eligible women to participate in the longitudinal evaluation of the study. Women who agree to take part will be asked to sign an informed consent form and two CATI (computer assisted telephone interview) will be scheduled for 3 and 6 months postpartum plus a medical visit with the woman and the newborn infant six months following delivery.

For the control group, all women admitted to the hospital for obstetric care in the same facility on the same day on which a case has been identified and who have none of the conditions indicating severity will be eligible. Following a process of randomized selection balanced according to mode of delivery, maternal age and gestational age at the time of delivery, women in the control group will be invited to participate in the study by the research assistants in the same way as candidates to the study group. Three months after delivery, the study call center will contact the women to carry out the first step in data collection. At the time of this contact, the interviewers will again go over the objectives of the study and will apply standard questionnaires designed to investigate quality of life and postpartum depression. This interview is estimated to last around 20 minutes.

At six months postpartum, the study call center will contact the women again to carry out the second step in data collection. At this contact, the interviewers will go over the study objectives once again and apply the same standard questionnaires on quality of life and postpartum depression, lasting no more than 20 minutes. In the case of women who do not have a telephone, a reminder letter will be sent asking them to phone the study call center at the sixth month postpartum to enable the interview to take place.

At the end of the 6-month telephone interview, the interviewer will confirm the date, time and place of the visit that was previously scheduled when the women were still in hospital. The women will be reminded that they should bring the baby to the visit. Even if they do not authorize the participation of their infants in the study, the women will be invited to return to the hospital and answer the questionnaires. The interview will be carried out by a trained female interviewer, who will apply standard questionnaires to evaluate posttraumatic stress disorder, sexual function and the woman's perception of her functional status in routine activities, taking no more than 35 minutes for each woman. After the mothers have answered the questionnaires, the weight, height and neuro-psychomotor development of the infants will be evaluated by a specially trained pediatrician, taking around 20 minutes. Finally, the women will receive a token cash payment as a contribution towards their transportation and food costs while attending this visit.

The following instruments will be used for data collection:

Posttraumatic Stress Disorder (PTSD) Checklist - Civilian Version (PCL-C)

This questionnaire has been validated in Brazil to screen for the diagnosis of posttraumatic stress disorder. It contains 17 items in which women will indicate to what extent she has been disturbed by symptoms over the past month on a scale of 1-5 (ranging from not at all to a lot). A score ≥ 3 (a medium score) for any one of the items is considered indicative of a clinically significant symptom.

Medical Outcomes Study 36-Item Short-Form Health Survey (SF36)

This is a generic questionnaire for evaluating quality of life that has been validated for use in Brazil. It is multidimensional with 36 items in 8 scales: physical functioning, role-physical, body pain, general health, vitality, social functioning, role-emotional and mental health. Final scores vary from 0 to 100 (poorest to best).

Female Sexual Function Index

A multidimensional questionnaire used to evaluate female sexual function consisting of 19 questions in 6 domains: desire, arousal, lubrication, orgasm, satisfaction and pain. Final scores vary from 2 to 36, a cut-off point < 26 having been proposed as determinant of sexual dysfunction. This questionnaire has been culturally adapted for use in Brazil.

Edinburgh Postnatal Depression Scale (EPDS)

A questionnaire used to screen for symptoms of depression and anxiety in the postpartum period, containing 10 questions that may be self-administered. A final score ≥ 10 has been defined as the cut-off point of greatest sensitivity in screening. The tool has been validated for use in Brazil.

The World Health Organization Disability Assessment Schedule II (WHODAS II)

A 36-item questionnaire used to evaluate the individual's perception of herself and her functional status, consisting of six activity domains related to the woman's routine activities (understanding and communicating, getting around, self-care, getting along with people, life activities in the home/at work and participation in society), on a 6-level scale varying from (1) no difficulty to (6) extreme difficulty/cannot do. Final score varies from 0 to 100 (from best to worst) [25].

Neuro-psychomotor development of the child

The Denver Developmental Screening Test II consists of 125 tasks or items organized in the form of tests of 4 general functions: personal-social, fine motor-adaptive, language and gross motor. At the end, a behavior test is applied that helps the examiner subjectively observe the overall behavior of the child and obtain an impression on how the child uses his/her skills.

Quality control

Quality control procedures will be adopted and include techniques such as reviewing completed forms, checking data entry, repeating data collection for selected medical charts and the use of a detailed manual of operation. Initial quality control of data collection will be performed by the local investigator prior to and during electronic data entry of the forms in order to identify any possible inconsistencies in the data.

A second quality control procedure will be carried out by one of the principal investigators, who will visit the participating centers. At this visit, consistency will be verified between the manual records on file and the data contained in the electronic forms. In addition, a random evaluation will be made of hospital records.

For the quality control of the longitudinal component, 10% of the records at each participating center will be randomly selected at the end of individual data collection and contact will once again be made with the patient in order to verify the data obtained at the first interview. The local investigators will maintain a record of any problems occurring during the study and any queries will be raised with the country coordinator of the project.

Data analysis

Data analysis will be performed in sub-groups according to the time of occurrence of the near-miss or severe maternal morbidity (in adolescence, older ages or at another time in the woman's reproductive life) and determining cause (hypertension, hemorrhage, abortion or other causes). The rates of maternal near-miss will be calculated for each collaborating center using the WHO maternal near miss approach [5], and frequencies of non-near-miss severe maternal morbidity will be calculated using specific defined diagnoses. General estimates will be calculated together with their respective 95% confidence intervals. The association between organ dysfunction and maternal death will be estimated using odds ratios, likelihood ratio test and their respective 95% confidence intervals. In addition, relative risks will be calculated for sexual dysfunction, postpartum depression, posttraumatic stress disorder, deterioration in quality of life, deterioration in the woman's perception of her own functional status in routine activities, risk of adverse perinatal outcome and risk of impaired neuromotor and weight-height development in the children born from the pregnancy associated with severe maternal morbidity.

Results obtained from the preliminary project

Initially, a meeting was held during the Brazilian national congress of Gynecology and Obstetrics in November, 2007, and attended by representatives of 35 healthcare facilities in Brazil. At this meeting, the main points featured in the initial concept of the project were presented and an invitation was made to institutions interested in participating in a Brazilian network on the topic. Those who were interested in participating filled out a registration form with the addresses and characteristics of their respective healthcare institutions. In December 2007, an electronic form was sent to them to be completed with specific information. In accordance with the data received, 27 of these candidate healthcare institutions were selected to participate in the network, taking regional characteristics, geographic distribution, level of complexity and the number of deliveries performed into consideration.

In August 2008, a meeting with representatives from all the centers was held at the coordinating center in Campinas. At this meeting, the proposal was presented and discussed in detail, and suggestions were incorporated into the final version of the protocol. Participating center representatives were identified, the operational issues involved in implementing the study and the theoretical concepts were discussed, and the final version of the research project was defined. Concurrently, a signed commitment was undertaken by each representative to participate in the Brazilian Network for the Surveillance of Severe Maternal Morbidity: the Brazilian Network of Studies in Reproductive and Perinatal Health was created. A Steering Committee was also designated for the study.

Ethical aspects

The coordinating center has already obtained the approval of the local Institutional Review Board and of the National Council for Ethics in Research (CONEP) of the Brazilian Ministry of Health for both components of the project. The participation of the collaborating centers in this study will only be confirmed after the project has been approved by their respective Institutional Review Boards. Individual signed informed consent will not be requested from the women involved in the cross-sectional analysis, since this study does not involve any type of intervention that could adversely affect their treatment; the data of interest will be obtained retrospectively from the patient's charts and without identifying the woman. Therefore, a waiver of the requirement for signed informed consent was obtained. It is understood that there is no other way of obtaining concrete, reliable information on cases of severe maternal morbidity or death,

since these patients are unable to give their consent. However, informed consent will be obtained from the women involved in the longitudinal component of the study. All the principles regulating research in human beings will be respected.

Based on the questionnaires applied, women diagnosed with some type of pathological condition, who are not receiving medical care, will be referred to healthcare facilities equipped to provide them with follow-up care. Women who have already received a diagnosis of a pathological condition but are not being followed up by a physician will also be referred to an appropriate healthcare service.

Technical and scientific contributions expected from the project

Brazil is a country with very high proportion of births taking place in health facilities (around 97%). The results of the present study will permit a prospective evaluation of severe maternal morbidity and deaths nationwide through the participation of healthcare facilities with different regional characteristics. No multicenter collaborative studies of this dimension are currently being carried out in healthcare institutions in Brazil in the field of Reproductive Health, and no data thus obtained are currently available. In addition to the specific study of maternal health hazards, the organizational structure required by this project will guarantee continuity of the investigation into various conditions of interest to public health beyond the period in which this study will be conducted. The implementation of a collaborative network is essential for expanding the production of substantive research in the field of maternal and perinatal health in Brazil.

Certainly, the availability of resources for the implementation and development of the Brazilian Network for the Surveillance of Severe Maternal Morbidity will lead to new scientific findings relevant to Brazil and other countries. Concomitantly, this will permit the construction of an innovative technological base from which health data may be obtained on a continuous basis, providing the evidence required to institute a real and effective improvement in the quality of life and health of the population. This network is committed to participating in future collaborative studies in the areas of perinatal and women's healthcare. The implementation of a series of multicenter studies is anticipated in this area in a way never before achieved in this country. This fact gives greater power to the results, which will therefore be more representative of the country, a particularly interesting achievement bearing in mind the wide ethnic, cultural and social diversity of the Brazilian population.

We hope that this initiative contributes to the improvement of health care and for the reduction of maternal and perinatal morbidity and mortality.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The idea for the study arose in a group discussion with all authors. The first version of the protocol was drafted by JPS and JGC, then complemented with the suggestions of the others. RCP and RSC were responsible for including the initial proposal for a multidimensional evaluation of consequences. SMH was responsible for the final, complete version of the protocol. JGC supervised the whole process. All authors contributed to the development of the study protocol and approved the final version of the manuscript.

Appendix 1: Criteria defining Near-Miss (WHO)*

A woman who fulfills one of the following criteria and survives a complication during pregnancy, childbirth or in the 42 days postpartum should be considered a near-miss.

Clinical Criteria

Acute cyanosis

Breathing rate > 40 or < 6

Oliguria unresponsive to fluids or diuretics

Loss of consciousness for ≥ 12 hours

Unconscious, no pulse/heartbeat

Jaundice concomitantly with preeclampsia

Gasping

Shock

Coagulation disorders

Cerebrovascular accident

Total paralysis

Laboratory Criteria

Oxygen saturation <90% for > 60 minutes

Acute thrombocytopenia (<50,000 platelets)

Creatinine ≥ 300 μmol/l or ≥ 3.5 mg/dL

Bilirubin >100 μmol/l or > 6.0 mg/dL

Unconscious, presence of glucose and ketoacidosis in urine.

Lactate > 5PaO2/FiO2 < 200

pH < 7.1

Management Criteria
Use of continuous vasoactive drug

Dialysis for treatment of acute kidney failure

Puerperal hysterectomy due to infection or hemorrhage

Cardiopulmonary resuscitation (CPR)

Transfusion ≥ 5 units of red blood cell concentrate

Intubation and ventilation for a period ≥ 60 minutes, unrelated to anesthesia*

Modified from [5]

Appendix 2: Indicators of non-near-miss severe maternal morbidity (potentially life-threatening conditions) *

Hemorrhagic disorders
Abruptio placentae

Placenta accreta/increta/percreta

Ectopic pregnancy

Antepartum hemorrhage

Postpartum hemorrhage

Ruptured uterus

Abortion with severe hemorrhage

Hypertensive disorders
Severe Preeclampsia

Eclampsia

Severe hypertension

Hypertensive encephalopathy

HELLP syndrome

Other systemic disorders
Endometritis

Pulmonary edema

Respiratory failure

Seizures

Sepsis

Thrombocytopenia <100,000

Thyroid crisis

Management indicators of severity
Blood transfusion

Central venous access

Hysterectomy

ICU admission

Prolonged hospital stay (>7 postpartum days)

Intubation not related to anaesthetic procedure

Return to operating room

Major surgical intervention

*Modified from [5]

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