ELVIRA AMÉLIA DE OLIVEIRA ZANETTE

NEAR MISS E MORTE MATERNA EM MULHERES COM DISTÚRBIOS HIPERTENSIVOS GRAVES: ESTUDO MULTICÊNTRICO NO BRASIL

NEAR MISS AND MATERNAL DEATH IN WOMEN WITH SEVERE HYPERTENSIVE DISORDERS: MULTICENTER STUDY IN BRAZIL

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Orientadora: Profª. Drª. MARY ANGELA PARPINELLI

NEAR MISS AND MATERNAL DEATH IN WOMEN WITH SEVERE HYPERTENSIVE DISORDERS: MULTICENTER STUDY IN BRAZIL

Dissertação de Mestrado apresentada ao Programa de Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do Título de Mestra em Ciências da Saúde, na área de concentração em Saúde Materna e Perinatal.

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Dedico este trabalho...

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Sumário

Símbolos, Siglas e Abreviaturas

AVC – Acidente Vascular Cerebral

CAV – Condição Ameaçadora de Vida

CAISM – Centro de atenção Integral à Saúde da Mulher

CEMICAMP – Centro de Pesquisas em Saúde Reprodutiva de Campinas

CEP – Comitê de Ética em Pesquisa

CID-10 – Classificação Estatística Internacional de Doenças 10^0 revisão

CIVD – Coagulação Intravascular Disseminada

CMM – Comitê de Mortalidade Materna

CPAV – Condição Potencialmente Ameaçadora de Vida

DH – Distúrbio Hipertensivo

DHL – Desidrogenase lática

DPP – Descolamento Prematuro de Placenta

EAP – Edema Agudo de Pulmão

HC – Hipertensão Crônica

HELLP – *Hemolysis Elevated Liver Enzymes Low Platelet*

HG – Hipertensão Gestacional

IC – Intervalo de Confiança

IM – Índice de Mortalidade

MMG – Morbidade Materna Grave

MM – Mortalidade Materna

NV – Nascidos Vivos

NMM – *Near Miss* Materno

OMS – Organização Mundial de Saúde

PaO_2 – Pressão Parcial de Oxigênio

FiO_2 – Fração inspirada de Oxigênio

PE – Pré-eclâmpsia

PH – Potencial Hidrogeniônico

RCP – Ressuscitação Cardiopulmonar

RCPAV – Razão de Condição Potencialmente Ameaçadora de Vida

RDMG – Razão de Desfecho Materno Grave

RMM – Razão de Morte Materna

RNMM – Razão de *Near Miss* Materno

RNVMMG – Rede Nacional de Vigilância de Morbidade Materna Grave

RP – Razão de Prevalência

RP aj – Razão de Prevalência ajustada

SOFA – *Sequential Organ Failure Assessment*

TGO – Transaminase Glutâmico Oxalacética

UNICAMP – Universidade Estadual de Campinas

UNICEF – *United Nations Children`s Emergency Fundantion*

UTI – Unidade de Tratamento Intensivo

WHO – *World health Organization*

Resumo

I**ntrodução**: Estima-se que os distúrbios hipertensivos (DH) na gravidez causem 50.000 mortes maternas (MM) a cada ano e que a imensa maioria ocorra em países de baixa ou média renda, além de aumentarem de 3 a 25 vezes o risco de complicações graves. Nas duas últimas décadas, tem sido crescente o interesse em estudar a morbidade materna grave (MMG)/*near miss* (NM) como método complementar às auditorias e inquéritos sobre MM. A investigação do NM é capaz de fornecer mais detalhes sobre fatores que contribuem para ambos, mortalidade e morbidade grave e uma referência para avaliação da qualidade do cuidado obstérico. **Objetivo**: identificar a prevalência e os fatores associados ao NM/MM em uma população de mulheres com DH graves (pré-eclâmpsia grave, eclâmpsia, hipertensão arterial grave e síndrome HELLP). **Método:** estudo multicêntrico, envolvendo 27 maternidades de referência, participantes da Rede Nacional de Vigilância da Morbidade Materna Grave, localizadas nas cinco regiões do Brasil. Realizou-se vigilância prospectiva com dados coletados após o desfecho final do caso de todas as mulheres admitidas por MMG e selecionados para o estudo os casos de MMG por DH grave, no período de junho de 2009 a julho de 2010. Os dados foram coletados em

formulários específicos e digitados na plataforma *OpenClinics®*. Foram estudadas variáveis maternas sociodemográficas, obstétricas, clínicas, resultados perinatais e tipos de demora no cuidado obstétrico. Os casos foram classificados segundo os critérios da OMS em condição potencialmente ameaçadora da vida (CPAV) e NM/MM. Foi realizada análise bivariada pelo cálculo das razões de prevalência (RP) e seus respectivos intervalos de confiança (IC) de 95% ajustados pelo efeito conglomerado e análise múltipla por regressão de Poisson. O nível de significância adotado foi de 0,05%. **Resultados**: os DH graves foram a principal causa de MMG (6706/9555); a prevalência de NM foi 4,2 casos por 1000 (NV), a relação caso/fatalidade foi de 8,3 NM para 1 MM. A manifestação precoce da doença e a hemorragia pós-parto foram variáveis independentes associadas ao desfecho em NM/MM, além do edema agudo de pulmão, cardiopatia prévia e demoras no cuidado de segundo e terceiro tipos. **Conclusão:** o estudo do *near miss* identificou dentre as mulheres com DH graves situações independentemente associadas ao pior desfecho, e que pode ser modificado por intervenções no cuidado obstétrico direto a estas mulheres e no sistema de saúde. O estudo mostrou ainda a factibilidade de um sistema de vigilância hospitalar de MMG capaz de contribuir para a redução da MM.

Palavras-chave: mortalidade materna; *near miss* materno; falência ou disfunção orgânica; distúrbios hipertensivos graves; pré-eclâmpsia grave / eclâmpsia.

Summary

I**ntroduction**: It has been estimated that hypertensive disorders (HD) in pregnancy may cause 50.000 maternal deaths (MD) annually and the large majority occurs in low-income or middle-income countries. Furthermore, these disorders increase the risk of severe complications by 3 to 25 times. In the last two decades, there has been increased interest in the study of severe maternal morbidity (SMM)/*near miss* (NM) as a supplementary method to audits and enquiries about MD. The investigation of NM is able to offer more details about factors that may contribute to both mortality and severe morbidity and may be used as a reference for evaluating quality of obstetric care. **Objective**: to identify the prevalence and factors associated with NM/MD in a female population suffering from severe HD (severe preeclampsia, eclampsia, severe arterial hypertension and HELLP syndrome). **Method:** A multicenter study, involving 27 referral maternity hospitals, participating in the National Surveillance Network for Severe Maternal Morbidity, located in five Brazilian regions. A prospective surveillance was performed with data collected after final case outcome in all women admitted to hospital for SMM and selected for the study of SMM cases due to severe HD, from June 2009 to July 2010. Data were collected in specific forms and entered

into the *OpenClinics®* platform. Variables studied were maternal sociodemographic characteristics, obstetric and clinical history, perinatal results and types of delay in obtaining obstetric care. Cases were classified according to the WHO criteria: potentially life-threatening conditions (PLTC) and NM/MD. Bivariate analysis was performed by estimation of prevalence ratios (PR) and their respective 95% confidence intervals (CI) adjusted by the conglomerate effect and Poisson multiple regression analysis. The significance level adopted was 0.05%. **Results**: severe HD was the main cause of SMM (6706/9555); the prevalence of NM was 4.2 cases per 1000 (LB), the case/fatality rate was 8.3 NM to 1 MD and the MD index was 10.7%. Early manifestation of disease and postpartum hemorrhage were independent variables associated with outcome in NM/MD, in addition to acute pulmonary edema, previous heart disease and delays in receiving secondary and tertiary care. **Conclusion:** the near miss study identified severe conditions that were independently associated with a worse outcome among women with HD that could be modified by interventions in direct obstetric care of these women and in the healthcare system. The study also showed that a hospital surveillance system for SMM is feasible and can contribute to a reduction in MD.

Key words: maternal mortality; maternal near-miss; organ dysfunction or failure; hypertensive disorders; severe preeclampsia/eclampsia.

1. Introdução

A Organização Mundial de Saúde (OMS) define morte materna (MM), segundo expresso na Classificação Internacional de doenças – 10ª Revisão (CID-10) (1), como a morte de uma mulher durante a gestação ou até 42 dias após o término da mesma, independente da duração ou da localização da gravidez, devida a qualquer causa relacionada com ou agravada pela gestação ou por medidas tomadas em relação a ela, porém não devidas a causas acidentais ou incidentais (1,2). A Federação Internacional de Ginecologia e Obstetrícia (FIGO) recomenda que sejam consideradas, como mortes maternas, todas as mortes, independentemente da causa, que ocorram até 42 dias após o término da gestação, e todas aquelas em que tenha sido possível identificar, como desencadeante da causa, o processo gestacional, até um ano pós-parto. O conceito de morte materna tardia foi introduzido pela OMS em 1994, significando a morte de uma mulher por causas obstétricas diretas ou indiretas, ocorridas entre 42 dias até um ano depois do término da gravidez. As mortes maternas diretas resultam de complicações obstétricas relacionadas à gravidez, parto e puerpério, devidas a uma sequência de eventos resultantes de situações como hemorragia, infecção puerperal, hipertensão, tromboembolismo, acidente anestésico ou às intervenções,

omissões, tratamento incorreto. As mortes indiretas decorrem de doenças pré-existentes ou que se desenvolvem durante a gestação e que não se devem a causas obstétricas diretas, mas que foram agravadas pelos efeitos fisiológicos da gestação (cardiopatias, colagenoses e outras doenças crônicas) (2,3).

A mortalidade materna (MM) é uma das mais graves violações dos direitos humanos das mulheres, por ser, em sua maioria, evitável e por ocorrer, principalmente, nos países de baixa renda, que são responsáveis por 86% dos nascimentos em todo o mundo, onde acontecem 99% dos óbitos maternos (3). Atualmente, em muitos países de alta renda, a RMM é menor que 10 por 100.000 NV. Nas Américas, essa disparidade entre países de alta e baixa renda fica mais evidente ao compararmos Canadá e EUA que apresentam valores inferiores a 11 óbitos maternos por 100.000 nascidos vivos (NV), enquanto em países, como a Bolívia e o Peru, o número chega a 200 óbitos maternos por 100.000 NV e, no Haiti, chega a 670 óbitos por 100.000 NV (2,4). A MM pode ser um indicador da decisão política de garantir saúde a esta parcela da população (4). Tal indicador de saúde pública é o que melhor demonstra as diferenças sociais entre países e entre regiões de um mesmo país (5). De acordo com a OMS e o United Nations Children`s Emergency Fund (UNICEF), a MM representa um indicador do status da mulher, seu acesso à assistência à saúde e adequação do sistema em responder às suas necessidades (3).

A Organização Mundial da Saúde (OMS), em 2003, estimou que, anualmente, 20 milhões de mulheres apresentaram complicações agudas da gestação, com a ocorrência de 529 mil óbitos (6). Novas estimativas foram publicadas em setembro

de 2011, projetando a ocorrência de aproximadamente 273 mil mortes em todo o mundo. Essas são estimativas independentes, de governos ou das Nações Unidas. Tal redução é importante não só pelo número de mortes evitadas, como também é um indicador robusto do grau de desenvolvimento humano, econômico e social (7).

No Brasil, o óbito materno, provavelmente sub-notificado, foi estimado, em 2002, na razão de 73 por 100 mil NV, com importante avanço na redução da MM, já que o patamar era de 140 mortes maternas por 100 mil nascidos vivos, em 1990 (6). De 1990 a 2010, as mortes maternas caíram 51% no Brasil, passando de 120 para 56 por 100 mil nascimentos. É o que aponta relatório da Organização Mundial da Saúde (OMS), do Fundo das Nações Unidas para a Infância (Unicef), Fundo de População das Nações Unidas e o Banco Mundial (OMS, 2010). Segundo o relatório, 50 países apresentaram resultados positivos relacionados à redução da mortalidade materna, entre eles o Brasil. A meta é alcançar a taxa de 35 mortes maternas para cada 100 mil nascidos vivos até 2015. Os dados mais recentes do Ministério da Saúde apresentam queda menor em comparação aos das Nações Unidas. De 1990 a 2010, a taxa caiu de 141 para 68 mortes de mulheres para 100 mil nascidos vivos, conforme a pasta divulgou em fevereiro deste ano (MS). A queda ocorreu com mais intensidade até o início dos anos 2000. Desde então, o ritmo tem sido mais lento (7). No primeiro semestre do ano passado, foram registradas 705 mortes maternas, ante 870 no mesmo período de 2010 – uma redução de 19%, de acordo com levantamento parcial.

Em 2008, o Ministério da Saúde assumiu o gerenciamento das investigações das mortes de mulheres em idade fértil – entre 10 e 49 anos. Todos os casos são

analisados por equipes de vigilância dos estados e dos municípios, e as informações repassadas ao órgão federal. A intenção é avaliar as causas e circunstâncias da morte e verificar se os casos foram gerados por complicações gestacionais. Para melhorar o acesso, a cobertura e a qualidade da atenção à saúde materna, principalmente às gestantes de risco, a notificação está sendo aperfeiçoada com o novo Sistema Nacional de Cadastro, Vigilância e Acompanhamento da Gestante e Puérpera para Prevenção da Mortalidade Materna. Também está prevista a criação de comissões responsáveis por manter atualizadas as informações cadastrais de todas as gestantes atendidas pela referida unidade de saúde (Blog da Saúde/MS).

Na “Declaração do Milênio”, compromisso firmado em 2000, pelos líderes dos Estados Membros das Nações Unidas, visando combater a pobreza e promover o desenvolvimento, dos oito objetivos a serem alcançados até 2015, três são relacionados à saúde, sendo um dirigido à melhora da saúde materna, com o objetivo de reduzir a MM em ¾ até 2015 (8). O caráter evitável, da maioria dos casos de morte materna, revela falhas ou demoras, em diferentes momentos do cuidado obstétrico. Isto se deve äs dificuldades de acesso da mulher aos serviços de saúde até a inadequação no manejo de complicações obstétricas, nas unidades hospitalares (9). Primar pelo desenvolvimento social e pela melhor assistência na saúde, provavelmente, contribuirá para reduzir tal mortalidade (10,11). Sabe-se que, cerca de 70% das mortes maternas, são decorrentes de hemorragias, eclâmpsia, sepse e abortos inseguros, ou seja, causas obstétricas diretas, (12) que podem ser prevenidas através da organização de uma rede hierarquizada e adequada de cuidados (13, 14, 15,16,17).

Levando-se em conta as deficiências quantitativas e qualitativas das informações sobre MM, torna-se importante fonte de informações, o estudo de mulheres que sobreviveram às severas complicações da gravidez (9, 18, 19, 20). Para cada caso de morte materna, um maior número de mulheres sobrevive a complicações graves podendo apresentar sequelas permanentes. Seus recém-natos também apresentam alta morbimortalidade (21,22,23). Tal grupo de mulheres é importante para o melhor entendimento da evolução de uma gravidez normal passando por uma complicação grave até a morte materna, além de possibilitar acesso às informações sobre o atendimento das mesmas (24).

Conceitualmente, há um espectro de severidade clínica com dois extremos; de um lado, a gravidez saudável, e de outro, a morte materna. A sequência de eventos ou processos, que modificam a evolução natural de uma gravidez saudável para a morte materna, começa após uma injúria clinica que pode ser acompanhada por uma resposta inflamatória, seguindo-se uma falência ou disfunção orgânica, e finalmente a morte. (25).

Figura1. Evolução clínica para *Near Miss (OMS, 2009).*

Diferentes terminologias já foram utilizadas como sinônimas para conceituar as complicações graves ocorridas no ciclo grávido-puerperal, tais como morbidade materna grave (MMG), morbidade obstétrica e *near- miss* materno (NMM). A terminologia *near miss,* ou quase perda, foi adaptada pelas ciências médicas de um conceito usado na indústria aeronáutica. Este descreve um evento de quase colisão entre aeronaves por aproximação indevida e que, apenas não ocorreu, por sorte ou por manejo adequado (26). No estudo da morbidade materna, o conceito de *near-miss*, introduzido por Stones et al, se refere às situações em que as mulheres, por apresentarem complicações potencialmente letais durante a gravidez, parto ou puerpério, sobrevivem devido ao acaso, ou ao cuidado obstétrico (27,28).

Os determinantes primários desta morbidade materna grave são os mesmos da MM, fato que possibilita identificar falhas ou dificuldades na assistência obstétrica (14, 17,28, 29, 30).

Existem três maneiras de diagnosticar a MMG: pelo critério clínico relacionado a uma doença específica, por uma intervenção realizada, ou pela presença de uma disfunção/falência orgânica (31). A falta de uniformidade nos critérios diagnósticos de MMG dificulta o acesso a dados reais sobre a prevalência da mesma, influenciando as estimativas do problema (32,33,34).

Recentemente, a OMS referendou a investigação do *near miss* como um padrão para o monitoramento do cuidado da saúde materna e padronizou, além do conceito e da definição (“a mulher que estando próxima da morte sobrevive a uma complicação que ocorreu durante a gravidez, parto ou até 42 dias do término da gestação”) (9,35), os critérios para o diagnóstico valorizando a

presença de disfunção ou falência orgânica, verificada a partir de três grupos de critérios (clínicos, laboratoriais e de manejo) (9,17) (Anexos 2,3). Classificou as complicações no ciclo grávido puerperal, segundo uma linha evolutiva de gravidade, em condições potencialmente ameaçadoras da vida (CPAV) (anexos 2,3) e condições ameaçadoras da vida (CAV). Este último, formado pelos casos de *near miss* e por aqueles que evoluíram do *near miss* para a morte materna. Definiu, ainda, indicadores do cuidado obstétrico baseados no near miss e na morte materna (9,36) (Anexo 4).

Os distúrbios hipertensivos (DH) complicam cerca de 6 a 8% de todas as gestações e são importantes causas de morte materna (37). Em todo o mundo, 10% a 15% das mortes maternas por causa direta estão associadas à pré-eclâmpsia e eclâmpsia (38). A pré-eclâmpsia pode ainda, levar às sequelas cardiovasculares (39), além de sequelas pós-traumáticas, principalmente se essas mulheres permanecem doentes, tem partos prematuros ou seus filhos morrem (38,40).

As causas da maior parte dos casos de hipertensão durante a gravidez, particularmente a pré-eclâmpsia, permanece desconhecida (37), assim como sua real prevalência, já que no mundo, a maioria das mortes relacionadas à pré-eclâmpsia ocorrem em mulheres que não tiveram acesso aos serviços de saúde (41). Como complicações da pré-eclâmpsia podemos ter a eclâmpsia, falência renal, descolamento prematuro de placenta (DPP), choque, coagulopatias, edema agudo de pulmão, AVC, natimortalidade, restrição de crescimento intrauterino e prematuridade (42).

Segundo o National High Blood Pressure Education Program Working Group on Blood Pressure in Pregnancy (2000), esses distúrbios podem ser Hipertensão Gestacional (HG), Hipertensão Crônica (HC), Pré-eclâmpsia (PE) isolada ou superposta e Eclâmpsia (E), de acordo com a fase gestacional em que aparecem os sintomas, se existe proteinúria e a gravidade do quadro (37).

A despeito dos avanços no entendimento da fisiopatologia da pré-eclâmpsia, o parto/dequitação da placenta, continua sendo a única cura para a doença (43). Quando a pré-eclâmpsia aparece precocemente na gestação, nem sempre o parto é a melhor opção para o feto (44), levando-nos ao dilema da conduta expectante.

O grupo de pesquisa de morbidade materna grave (MMG) da Universidade Estadual de Campinas (Unicamp), baseado no interesse mundial dos pesquisadores sobre os casos de "*near-miss"*, criou a Rede Brasileira de Estudos em Saúde Reprodutiva e Perinatal, na data de 4 de agosto de 2008, em Campinas, iniciativa conjunta do Departamento de Tocoginecologia, do Centro de Atenção Integral à Saúde da Mulher (CAISM) da Unicamp e intermediado pelo Centro de Pesquisas em Saúde Reprodutiva de Campinas (Cemicamp) (45) (Anexo 5).

O objetivo maior dessa rede consiste em estruturar uma iniciativa de colaboração nacional, entre centros de referência, para cooperar no desenvolvimento de projetos relacionados à saúde materna, reprodutiva e perinatal. Hoje, 27 centros participam dessa rede, distribuídos pelo território nacional, englobando os estados do Amazonas, Ceará, Pernambuco, Bahia, Minas Gerais, São Paulo, Rio de Janeiro, Rio grande do Sul, Paraná, Paraíba, Maranhão e Goiás. Tais centros cooperaram na formação de um banco de

dados, objeto do projeto “Rede Brasileira de Vigilância de Morbidade Materna Grave” (RBVMMG) (45) (Anexos 2,3).

Na Rede (RBVMMG), foram compilados os dados referentes a aspectos sócio- econômicos e demográficos, antecedentes obstétricos e dados da gestação atual, das mulheres com complicações graves na gestação, parto e até 42 dias de puerpério, bem como indicadores clínicos, laboratoriais, manejo de gravidade, demoras e desfecho materno e perinatal (45).

Frente à relevância do estudo da morbidade materna e o elevado percentual dos distúrbios hipertensivos, como causa de morbidade e óbito materno, a proposta deste estudo foi, a partir dos dados da Rede Brasileira de Vigilância da Morbidade Materna Grave, estudar a prevalência e fatores associados ao *near miss* (NM) e morte materna (MM) em mulheres com distúrbios hipertensivos (DH) graves.

2. Objetivos

2.1. Objetivo geral

Conhecer a morbidade materna grave/*near miss* em mulheres com distúrbios hipertensivos graves (pré-eclâmpsia grave/eclampsia, síndrome HELLP, hipertensão arterial grave), ocorridos na gestação, parto e puerpério.

2.2. Objetivos específicos

- Identificar a prevalência de *near miss* materno em mulheres com distúrbios hipertensivos graves, na população de mulheres com morbidade materna grave;
- Calcular os indicadores do cuidado obstétrico para o grupo com DHG: RMM (razão de morte materna), RNMM (razão de *near miss* materno), RDMG (razão de desfecho materno grave), NMM: MM (relação *near miss* materno: morte materna) e IM (índice de mortalidade) neste grupo de mulheres;
- Identificar e estimar a associação de fatores sócio-demográficos, reprodutivos e comorbidades sobre o desfecho para NM e MM;

- Identificar e estimar a associação entre as variáveis da gestação atual e as demoras sobre o desfecho para NM e MM;
- Identificar complicações perinatais e estimar a associação de complicações clínicas sobre o desfecho para NM e MM;
- Identificar a prevalência de uso de Sulfato de Magnésio neste grupo de mulheres.

3. Sujeitos e Método

3.1. Desenho do estudo e local da realização

Estudo multicêntrico, envolvendo 27 maternidades de referência, participantes da Rede Nacional de Vigilância da Morbidade Materna Grave, localizadas nas cinco regiões do Brasil. Realizou-se vigilância prospectiva com dados coletados após o desfecho final do caso de todas as mulheres admitidas por MMG e selecionados para o estudo os casos de MMG por DH grave, no período de junho de 2009 a julho de 2010. Os dados foram coletados em formulários específicos e digitados na plataforma *OpenClinics®*. Foram estudadas variáveis maternas sociodemográficas, obstétricas, clínicas, resultados perinatais e tipos de demora no cuidado obstétrico. Os casos foram classificados segundo os critérios da OMS em condição potencialmente ameaçadora da vida (CPAV) e NM/MM. Foi realizada análise bivariada pelo cálculo das razões de prevalência (RP) e seus respectivos intervalos de confiança (IC) de 95% ajustados pelo efeito conglomerado e análise múltipla por regressão de Poisson. O nível de significância adotado foi de 0,05%.

3.2. Tamanho amostral

Para determinar o número de centros colaboradores a serem incluídos no estudo original da RBVMMG, considerou-se o número de nascimentos necessários para se identificar casos de NMM e MM. Estudos prévios estimaram a incidência de NMM de 8 casos por 1000 nascimentos e RMM no Brasil de 140 por 100.000 NV. Assim, 75.000 nascimentos seriam necessários para identificar 600 NMM e 100 MM. Tais números seriam suficientes para avaliar os critérios de NMM estabelecidos pela OMS em 2009 (13).

Para o estudo em questão considerou-se a prevalência de 67,7% de morbidade materna grave/near miss por causas hipertensivas em uma cidade da região sudeste do Brasil (Lotufo et al, 2012).

Considerando um nível de significância de 5% e um erro amostral de 2,5% (prevalência: 65,2% a 70,2%) seriam necessárias n = 1344 casos.

A amostra foi constituída por 6.706 casos de MMG por distúrbios hipertensivos graves do total de 9.555 casos, em banco informatizado e foi suficiente para o estudo em questão.

3.3. Definições e Conceitos

- Pré-eclâmpsia grave: presença de PA ≥ 160/110 mmHg e ou sintomatoloia associada a envolvimento de órgãos alvo e/ou proteinúria de 24h ≥ 2,0g / fita urinária ≥ 2+ associado a um dos seguintes sinais e sintomas:
  - Oligúria (< 30 ml/h por 2 horas);

- Distúrbios visuais (borramento visual ou escotomas cintilantes) e cefaleia;
- Epigastralgia / dor em quadrante superior direito do abdome;
- Trombocitopenia (menor que 100.000 plaquetas/mm^3);
- Edema pulmonar (acúmulo anormal de líquido nos pulmões).

– Eclâmpsia: convulsões tônico-clônicas generalizadas e/ou coma como manifestação do envolvimento cerebral, na pré eclâmpsia, não relacionada a qualquer outra condição patológica (neurológica ou sistêmica).

– Hipertensão grave: nível pressórico ≥ 160 x 110 mm de Hg ou pico hipertensivo de qualquer valor, porém associado a sintomas ou sinais de lesão de órgão alvo como cefaléia intensa, edema de papila, alterações visuais, precordialgia, alterações do nível de consciência ou necessidade do uso de drogas hipotensoras intravenosas para controle dos níveis pressóricos e/ou sintomas.

– HELLP síndrome: presença de pelo menos um dos critérios: hemólise (esfregaço periférico anormal, esquizócitos, aumento de DHL ≥ 600 U/L, aumento de bilirrubina total ≥ 1,2 mg/dl), elevação de enzimas hepáticas (ou aumento isolado de TGO ≥ 70 U/l) e plaquetopenia (<100.000/mm3). Deverá ser referido como HELLP os casos de HELLP parcial, que são aqueles onde pelo menos um dos critérios diagnósticos está presente, e a condução do caso clínico foi norteada a partir desse diagnóstico.

– **Critérios de Near miss (OMS):**

A presença de 1 ou mais critérios clínicos e/ou laboratoriais e/ou de manejo definem um caso de *near miss*.

Clínicos:

- Cianose;
- *Gasping*: padrão respiratório terminal e com respiração ruidosa;

- Frequência respiratória >40 ou < 6 ipm;
- Choque: hipotensão grave persistente (PA sistólica < 90 mmHg por ≥60 minutos com FC ≥ 120 bpm) apesar de reposição volêmica agressiva (> 2 litros);
- Oligúria: definida como um débito urinário < 30 ml/h durante 4 horas ou < 400 ml/24h;
- Distúrbios de coagulação: pode ser avaliada pelo teste de coagulação à beira do leito ou ausência de coagulação de acessos venosos após 7-10 minutos. Teste de coagulação à beira do leito: Um teste clínico para avaliar o estado da coagulação. Instruções: (1) Colete 2 ml de sangue venoso em um tubo seco de vidro (cerca de 10 mm x 75 mm); (2) Segure o tubo para o manter aquecido (+ 37 ° C), (3) Depois de 4 minutos, incline o tubo lentamente para ver se está formando um coágulo. Então, inclíne-o novamente a cada minuto até que o sangue coagule e o tubo possa ser girado de cabeça para baixo; (4) A não formação de um coágulo após 7 minutos ou a formação de um coágulo frágil, que se rompe facilmente, sugerem coagulopatia;
- Perda de consciência: uma profunda alteração do estado mental que envolve a completa ou quase completa falta de resposta a estímulos externos. É definida como uma Escala de Coma Glasgow <10 (coma moderado ou grave), por período > 12horas;
- Perda consciência e ausência de pulso/batimento cardíaco;
- AVC: é um déficit neurológico de causa vascular cerebral que persiste após 24 horas ou é interrompido pela morte dentro de 24 horas;
- Convulsão não-controlada: Condição na qual o cérebro está em um estado de permanente convulsão. Equivalente ao status epilepticus, normalmente definido como uma convulsão contínua e ininterrupta que durem mais de 30 minutos, ou crises recorrentes sem recuperação

da consciência entre as convulsões por mais de 30 minutos. Refratária, convulsão persistente;

- Icterícia na presença de pré-eclâmpsia: Pré-eclâmpsia: é definida como a presença de hipertensão associada à proteinúria. A hipertensão arterial é definida como uma pressão arterial ≥ 140 mm Hg (sistólica) ou ≥ 90 mmHg (diastólica) em pelo menos duas ocasiões entre 4-6 horas, após a 20ª semana de gestação em mulheres conhecidas como normotensas antecipadamente. Proteinúria é definida como excreção ≥ 300 mg de proteína em 24 h. Se urina de 24h não for disponível, a proteinúria é definida como uma concentração ≥ 300 mg / L (≥ 1 + na fita urinária) em pelo menos duas amostras de urina colhidas aleatoriamente, com intervalo de pelo menos 4-6h.

Laboratoriais

- Saturação de O_2 < 90% por >60 min;
- Relação PaO2/FiO2 < 200: relação entre a saturação arterial de oxigênio (PaO2) e a fração inspirada de oxigênio (FiO2). A saturação arterial de oxigênio é determinada pela realização de uma gasometria arterial. A fração inspirada de oxigênio pode variar de acordo com o paciente e deve ser gravada no momento da coleta de sangue para a gasometria. Pode ser precisa (por exemplo, durante a ventilação mecânica, 0,21 -1,00) ou estimada (sem suplementação de oxigênio, 0,21; cateter nasal de oxigênio, 0,25; facial máscara de oxigênio, 0,25-1,0);
- Creatinina ≥ 300 mmol/i ou ≥ 3,5 mg/dl;
- Bilirrubina ≥ 100 mmol/l ou ≥ 6 mg/dl;
- pH < 7,1;
- Lactato > 5;
- Plaquetas < 50.000 /mm^3;
- Presença de glicosúria e cetonúria (com perda de consciência).

Manejo

- Uso contínuo de droga vasoativa: O uso contínuo de qualquer dose de dopamina, adrenalina e noradrenalina. No contexto da infusão de drogas vasoativas, refere-se à infusão contínua e ininterrupta de uma solução contendo um fármaco vasoativo. Ela opõe-se à injeção em bolus ou intermitente de um fármaco vasoativo;
- Histerectomia por infecção ou hemorragia: exérese do útero logo após o nascimento ou nos dias subsequentes com o objetivo de preservar a vida da puérpera, em função de sepse grave ou hemorragia importante;
- Transfusão sanguínea: reposição volêmica com derivados hemodinâmicos ≥ 5 U de concentrado de hemácias;
- Ventilação mecânica invasiva por tempo igual ou superior a 60 minutos não relacionada à anestesia;
- Diálise para insuficiência renal aguda: processo artificial que serve para retirar, por filtração, todas as substâncias indesejáveis da circulação;
- Ressuscitação cardio-pulmonar: Refere-se a um procedimento de emergência médica para atendimento de uma vítima de parada cardíaca, incluindo compressões tórax e ventilação pulmonar.

3.4. Variáveis

3.4.1. Variáveis dependentes

Consideradas para o desfecho materno em:

– **Condições potencialmente ameaçadoras da vida**

Condições clínicas (diagnósticos clínicos), laboratoriais e de manejo que indicam a situação de gravidade, na ausência de um marcador ou critério de disfunção/falência orgânica durante a gravidez, parto e puerpério.

– ***Near miss* materno**

Mulheres que sobrevivem às complicações durante a gestação, parto e puerpério, apresentando qualquer um dos critérios ou marcadores, clínicos, laboratoriais ou de manejo, que identifiquem disfunção/falência orgânica.

– **Óbito materno**

Definido como o óbito de uma mulher durante a gestação, parto ou até 42 dias após o término da mesma, independente da duração ou da localização da gravidez. No presente estudo foi considerado o óbito acontecido durante a internação.

3.4.2. Variáveis independentes

Características maternas sócio-demográficas, reprodutivas, perinatais, antecedentes mórbidos, complicações e demoras:

– Idade (anos completos): categorizada para análise bivariada ≤19 20 a 29, 30 a 39 e ≥40 anos;

– Cor (conjunto de características socioculturais e fenotípicas, identificadas pela observação ou declaração da própria mulher). Categorizadas em: branca (mulheres de cor de pele branca ou parda de origem latino-americana) e não branca (Negra: mulheres que apresentarem cor da pele preta ou parda de origem africana. Amarela: mulheres de origem oriental-leste e sudeste asiático. Indígena: mulheres com características originárias da população autóctone do país, que se estabeleceu anteriormente ao processo de colonização, ou que vivam em comunidades indígenas);

– Escolaridade (número de anos estudados declarados pela mulher). Categorizada: ensino até fundamental completo e ensino maior que o fundamental;

– Estado marital (condição de a mulher conviver maritalmente). Categorizada: com companheiro e sem companheiro;

– Cobertura financeira no pré-natal (forma majoritária de financiamento do atendimento médico-hospitalar). Categorizada: pública e outra (privada, seguro saúde, plano de saúde);

– Cobertura financeira da internação (forma majoritária de financiamento do atendimento médico-hospitalar). Categorizada: pública e outra (privada, seguro saúde/plano de saúde);

– Tipo de acesso ao serviço de saúde (maneira como a mulher deu entrada à maternidade de referência). Categorizada em: procura espontânea (quando a chegada ao serviço de saúde ocorreu através de meios próprios da paciente ou de parentes, independentemente da situação de admissão ou gravidade), outra (transferência por serviço de resgate/emergência: quando a chegada ao serviço de saúde ocorreu através de transporte e equipe de emergência como SAMU, bombeiros, resgate, etc., acionados pela própria paciente, parentes, amigos ou socorristas). A transferência ainda pode ser programada:- comunicação entre as unidades e aceitação do caso para avaliação/admissão pelo centro de referência; e não programada:- quando a transferência entre hospitais ocorreu sem a aceitação prévia ou conhecimento do caso pela instituição receptora, ou quando na "vaga zero" pelo serviço de regulação de vagas sem que houvesse leito ou capacidade programada disponível para a aceitação do caso;

– Número de gestações (número total de gestações da mulher, incluindo gestações que terminaram em aborto, prenhez ectópica ou gestação molar, inclusive a gestação atual em questão). Categorizada em: Uma, 2-3 e ≥ 4;

– Número de partos (número total de partos ocorridos após 20 semanas, incluindo partos vaginais, cesáreas e partos vaginais assistidos, excluindo a gestação em questão). Categorizada em: 0 , 1-2 e ≥ 3;

– Número de cesarianas (correspondeu ao antecente de parto por cesárea). Categorizada em: 0 e ≥1;

– Forma de início do trabalho de parto (maneira como o trabalho de parto se iniciou). Categorizada em: espontâneo, induzido, cesárea eletiva;

– Forma de resolução do parto (como foi ultimada a gestação: parto vaginal- aquele que se ultimou pela via vaginal sem uso de instrumental auxiliar; parto vaginal operatório – aquele no qual foi empregado qualquer instrumento ou procedimento complementar para a ultimação do parto, como fórceps, vácuo-extrator, versão cefálica). Categorizada em: cesárea e outra;

– Tipo do pré-natal (número de consultas efetuadas a partir do diagnóstico de gestação até o seu término, comparado pela idade gestacional). Categorizado em: inadequado e adequado;

– Idade gestacional na internação (número de semanas completas de gestação por ocasião da internação). Categorizada em: <22 semanas, 22 a 27 semanas, 28 a 33 semanas, 34 a 36 semanas, ≥ 37 semanas, admissão pós-parto ou pós-aborto;

– Idade gestacional na resolução (número de semanas completas de gestação por ocasião da ultimação da gestação): Categorizadas em: <22 semanas, 22 a 27 semanas, 28 a 33 semanas, 34 a 36 semanas, ≥ 37 semanas, ou ainda grávida;

– Índice de Apgar do 5º minuto de nascimento. Categorizado em: <7 e ≥7;

– Peso do RN: peso ao nascer em gramas. Categorizado em: <2.500 g e ≥ 2.500 g;

– Condição de nascimento (avaliação da condição de vitalidade ao nascer). Categorizado em: natimorto e nativivo;

– Desfecho neonatal (condição do RN avaliada durante o período de internação). Categorizada em: alta, morte ou internado;

– Descolamento prematuro de placenta (separação da placenta, normalmente inserida, em gestação superior a 22 semanas). Categorizada em: sim e não;

– Hemorragia pós-parto (sangramento ocorrido após o nascimento, estimado por perda sanguínea ≥ 500 ml após parto vaginal ou ≥ 1.000 ml, ou necessidade de transfusão de hemoderivados). Categorizada em: sim e não;

– Outra hemorragia grave (qualquer outro sangramento que ocorra no período gravídico-puerperal, de causa não obstétrica e que leve à instabilidade hemodinâmica, choque, procedimento cirúrgico de urgência ou necessidade de transfusão de hemoderivados, como epistaxe volumosa, hemorragias digestivas, entre outras). Categorizada em: sim e não;

– Edema pulmonar (acúmulo anormal de líquido nos pulmões. Presença de tosse seca e persistente, taquipnéia, taquicardia e estertores crepitantes pulmonares, tosse produtiva, franca dispnéia, secreção rósea e bolhosa pelo nariz e boca, hipoxemia e retenção de CO_2). Categorizada em: sim e não;

– Tromboembolismo (formação de trombo no leito vascular levando à oclusão do vaso e / ou desprendimento de trombo ou outros elementos -líquido amniótico, gordura - e migração para vaso à distância, causando sua oclusão. Fazem parte desse diagnóstico as seguintes condições: trombose venosa profunda-TVP, tromboembolismo pulmonar-TEP,

embolia gordurosa, embolia amniótica, embolização cerebral-AVC isquêmico secundário à embolização): Categorizada em:sim e não;

– Sepse (pelo menos um dos sinais da síndrome de resposta inflamatória sistêmica – 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, associado à infecção documentada ou suspeita e pelo menos 1 dos sinais de disfunção orgânica aguda secundária à infecção). Categorizada em: sim e não;

– Manejo de gravidade (procedimentos avançados para manutenção da vida) e definidos para:

  - Transfusão de hemoderivados < que cinco unidades de concentrado de hemácias: sim e não.
  - Admissão em UTI: sim e não.
  - Hospitalização > 7 dias: sim e não.
  - Ventilação mecânica invasiva não anestésica por tempo inferior a 60 minutos: sim e não.
  - Uso do sulfato de magnésio: sim e não.

– Demoras

A pesquisa de demoras no atendimento foi realizada através de dados presentes no prontuário médico e pela avaliação global do caso pelos investigadores e coordenadores locais, ainda pode ser obtida através de relatos da equipe que assistiu a mulher durante a internação.

Foi considerado “sim” na impressão positiva pelos pesquisadores ou equipe assistente para o problema ou quando houve relato da ocorrência do problema no prontuário. Considerado “não” quando de fato não houve indício de ocorrência de qualquer problema específico.

- Demoras referentes à paciente / familiares (demora na procura ao serviço de saúde, dificuldade geográfica de acesso ao serviço de saúde, recusa ao tratamento, pré-natal ausente oi inadequado, aborto inseguro): Categorizada em: sim e não.
- Demoras referentes ao serviço / sistema de saúde (falta de medicação, dificuldade no transporte, dificuldade da comunicação, ausência de hemoderivados, dificuldade na monitorização, falta de pessoal treinado, dificuldade no acesso ao pré-natal). Categorizada em: sim e não.
- Demoras referentes aos profissionais de saúde (demora no diagnóstico, demora no início do tratamento, manejo inadequado do caso, demora na referência ou transferência do caso). Categorizadas em: sim e não.

3.5. Seleção dos Sujeitos

A população de estudo foi formada por todas as mulheres internadas com diagnóstico de hipertensão arterial grave e/ou emergência hipertensiva, pré-eclâmpsia grave, eclampsia e síndrome HELLP parcial ou total. Na identificação dos casos foram usados critérios definidos pela OMS para morbidade materna grave/*near miss*.

3.6. Coleta de Dados

No estudo original, assistentes de pesquisa locais, denominados de coordenador e investigador, após revisão diária dos prontuários, pós-alta, separavam as de interesse para o estudo, ou seja: condições potencialmente ameaçadoras da vida, *near miss* materno e morte, sendo transcritos os dados

para o formulário de coleta manual (anexo 6). Para todos os sujeitos incluídos, os assistentes de pesquisa responderam às perguntas referentes à adequação da assistência e à ocorrência de demoras. Após a coleta manual dos dados, eles foram digitados em formulários eletrônicos abrigados na plataforma eletrônica do *Open Clinica*. O link para o site do Open clinica está disponível no website do CAISM www.caism.unicamp.br.

Mensalmente, as instituições participantes informaram, pelo website, através do investigador, o número de partos e o número de nascidos vivos ocorridos no mês anterior.

Todas as informações necessárias referentes ao uso da internet, preenchimento dos formulários, manual e eletrônico, acesso ao banco de dados particular de cada centro, padronização das definições diagnósticas, entre outras, estavam disponíveis no manual de operações.

3.7. Controle de Qualidade

O Banco de Dados da Rede foi alimentado com informações retiradas dos prontuários e dos cartões de pré-natal, repassados para o formulário de coleta manual pelos coordenadores e investigadores locais. Tais formulários de coleta manual foram transcritos para os eletrônicos. O processo de seleção de casos e preenchimento de formulários obedeceu a um Manual de Operações. Um primeiro controle de qualidade da coleta dos dados foi realizado pelos investigadores locais, antes e durante a digitação eletrônica das fichas, para

identificação de possíveis incongruências nos dados. O segundo controle de qualidade foi realizado através de visita às instituições participantes, por um dos pesquisadores principais da Rede. Nas visitas, foi verificada a compatibilidade entre os registros arquivados nas fichas manuais e eletrônicas e os prontuários médicos. Para tal, foram selecionados aleatoriamente alguns casos. O terceiro controle de qualidade foi realizado por aplicação de consistência lógica e revisão do banco.

3.8. Processamento e Análise de Dados

As mulheres com distúrbios hipertensivos graves foram classificadas, segundo o desfecho da internação, em condições potencialmente ameaçadoras da vida (CPAV), near miss materno (NMM) e morte materna (MM), de acordo com os critérios de disfunção e/ou falência orgânica, estabelecidos pela OMS (clínicos laboratoriais e de manejo).

Com os dados coletados, foram calculados os indicadores do cuidado obstétrico:

- RMM: numero de mortes maternas por 100.000 NV nas maternidades estudadas,
- RNMM: número de casos de near miss materno por 1.000 NV,
- RDMG: número de casos de near miss somados ao número de casos de morte materna por 1.000 NV,

– Relação NMM: MM (caso-fatalidade): número de casos de near miss para cada caso de MM,

– IM: número de morte materna dividido pelo número de casos de near miss somados aos de morte materna e expresso em percentagem.

Foi realizada análise bivariada para identificação de fatores associados com os desfechos através do cálculo das razões de prevalência (RP) e seus respectivos intervalos de confiança (IC) de 95%, ajustados pelo efeito do conglomerado (maternidades ou centros). Ao final foi realizada análise múltipla por regressão de Poisson, também delineada por conglomerado. O nível de confiança foi definido em 95% (nível de significância de 5%) e os softwares utilizados foram o SPSS® versão 17 (SPSS, Chicago, IL, USA) e o Stata versão 7.0 (StataCorp, College Station, Tx, USA).

3.9. Considerações Éticas

Foram seguidos todos os princípios que regulamentam as pesquisas em seres humanos, definidos pelo Conselho Nacional de Saúde (Resolução 196/96). Dispensou-se o Termo de Consentimento Informado, frente ao fato de os dados serem colhidos de prontuários pós-alta e não ter sido realizada nenhuma intervenção. O estudo foi aprovado pelos Comitês de Ética locais e pelo Conselho Nacional de Ética em Pesquisa com Seres Humanos - CEP: N^0 097/2009 (anexo 1).

4. Publicação

ONLINE MANUSCRIPT SUBMISSION & PEER REVIEW
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Corresponding Author	José Cecatti (Univesity of Campinas)
Contributing Authors	Elvira Zanette , Mary Parpinelli , Fernanda surita , Maria Costa , Samira Haddad , Maria Sousa , João Pinto e Silva , Joao Souza , for the Brazilian Network for Surveillance of Severe Maternal Morbidity Group
Abstract	Objectives: to identify the prevalence and factors associated with maternal near miss (NM) and maternal death (MD) in women with severe hypertensive disorders (HD). Design: a cross-sectional, multicentre study. Setting: 27 maternity hospitals in Brazil. Sample: 6706 women with severe HD. Method: a prospective surveillance of severe maternal morbidity with data collected from medical charts and entered into OpenClinica®, an online system, over a one-year period (2009 to 2010). Women with severe preeclampsia, severe arterial hypertension, eclampsia and HELLP syndrome were included in the study. They were grouped according to outcome in NM/MD and potentially life-threatening condition (PLTC). Main Outcome Measures: Prevalence ratios and 95% confidence intervals adjusted for cluster effect for maternal and perinatal variables and delays in receiving obstetric care were calculated. Poisson multiple regression analysis was performed. Results: severe HD was the main cause of SMM (6706/9555); the prevalence of NM was 4.2 cases per 1000 LB, the case/fatality rate was 8.3 NM to 1 MD. Early manifestation of the disease and postpartum haemorrhage were independent variables associated with the outcome NM/MD, in addition to acute pulmonary oedema, previous heart disease and delays in receiving secondary and tertiary care. Conclusion: in women with severe HD, the current study identified situations independently associated with a worse outcome, which could be modified by interventions in obstetric care and in the healthcare system. Furthermore, the study showed the feasibility of a hospital system for surveillance of SMM that is capable of contributing to the reduction in MD.
Keywords	organ dysfunction, organ failure, severe preeclampsia, eclampsia, maternal mortality, maternal morbidity
Methodology	OBSERVATIONAL STUDIES (e.g. cohort, case-controlled, epidemiology)

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Maternal near miss and death due to severe hypertensive disorders. A multicentre study in Brazil

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Abstract

Objectives: to identify the prevalence and factors associated with maternal near miss (NM) and maternal death (MD) in women with severe hypertensive disorders (HD).

Design: a cross-sectional, multicentre study.

Setting: 27 maternity hospitals in Brazil.

Sample: 6706 women with severe HD.

Method: a prospective surveillance of severe maternal morbidity (SMM) with data collected from medical charts and entered into *OpenClinica*®, an online system, over a one-year period (2009 to 2010). Women with severe preeclampsia, severe arterial hypertension, eclampsia and HELLP syndrome were included in the study. They were grouped according to outcome in NM/MD and potentially life-threatening condition (PLTC).

Main Outcome Measures: Prevalence ratios and 95% confidence intervals adjusted for cluster effect for maternal and perinatal variables and delays in receiving obstetric care were calculated. Poisson multiple regression analysis was performed.

Results: severe HD was the main cause of SMM (6706/9555); the prevalence of NM was 4.2 cases per 1000 LB, the case/fatality rate was 8.3 NM to 1 MD. Early manifestation of the disease and postpartum haemorrhage were independent variables associated with the outcome NM/MD, in addition to acute pulmonary oedema, previous heart disease and delays in receiving secondary and tertiary care.

Conclusion: in women with severe HD, the current study identified situations independently associated with a worse outcome, which could be modified by interventions in obstetric care and in the healthcare system. Furthermore, the study showed the feasibility of a hospital system for surveillance of SMM that is capable of contributing to the reduction in MD.

Keywords: organ dysfunction; organ failure; severe preeclampsia; eclampsia; morbidity maternal; maternal morbidity.

Introduction

It has been estimated that hypertensive disorders (HD) in pregnancy cause 50.000 maternal deaths (MD) annually in the world and the vast majority of them occur in low-income or middle-income countries.[1] The main cause of MD in Latin America and in the Caribbean is HD, accounting for approximately one-fourth of the total number of deaths.2

In high-income countries, such as the United States, the prevalence of hospital admissions due to HD in pregnancy increased significantly between 1998 and 2006, rising from 67.2 to 81.4 per 1.000 deliveries over that time period[3]. In Canada, HD is the third cause of antenatal hospitalization, with little variation in rates for a 10-year period, from 15.4 per 1000 deliveries in 1991 to 11.3 per 1000 deliveries in 2001.[4]

HD increase the risk of severe complications by 3 to 25 times, e.g. placental abruption, thrombocytopenia, disseminated intravascular coagulation (DIVC), acute pulmonary edema (APE), cerebrovascular disorders and other conditions, in comparison to women without hypertension.[3,5,6] The contrast between low or very low maternal mortality ratios (MMR) in high-income countries, compared to low-income or middle-income countries with high MMR has been attributed to the quality of obstetric care, patient access to hospitalization, qualification of health professionals and structural resources, including the input and availability of intensive care units.[7-9]

In this context, the United Nations has recognized that quality of care is of central importance in the strategy to improve maternal and infant health.[10] In the last two decades, there has been increasing interest in the study of severe maternal morbidity (SMM)/near miss (NM) cases as a supplementary method to audits and inquiries on MD.[11-13] The investigation of NM could furnish more details about factors contributing to both mortality and SMM [10-14] and may be a reference for quality assessment of obstetric care. Nevertheless, in the literature there is still a wide variety of criteria used to identify maternal NM cases. [14]

In 2009, the WHO defined concepts and standardized criteria to identify NM cases, after the identification of organ dysfunction and/or failure as the main determinants of severity. Clinical signs, laboratory tests and management interventions were used, all capable of diagnosing organ dysfunction or failure.[15] These criteria were previously validated by the WHO Working Group following markers of dysfunction and total maximum SOFA (sequential organ failure assessment) score, applied to an obstetric population.[15-17]

We proposed this study due to the high association between HD in pregnancy and severe obstetric/clinical complications, resulting in high rates of SMM/NM and MD. In addition, there is a lack of studies to date focused on severe morbidity as proposed by the WHO.[15] The purpose of the current study was to identify the prevalence and factors associated with the risk of maternal NM and MD in a female population with severe HD (severe preeclampsia, eclampsia, severe arterial hypertension and HELLP syndrome).[18]

Method

This was a multicentre study, based on 27 referral maternity hospitals located in the five Brazilian regions participating in the Brazilian Network for Surveillance of Severe Maternal Morbidity (SMM).[19] Local investigators from each maternity hospital carried out a prospective surveillance with data routinely collected, after final outcome in all women admitted to hospital because of a SMM episode. Data were first collected in specific forms and then entered into the online OpenClinica® platform. Details on the original study methods are already published elsewhere. [19,20]

This is an analysis of SMM cases due to severe HD among the total number of SMM during pregnancy and postpartum period, managed by these maternity hospitals, over a 12-month period, from July 2009 to June 2010. It included women diagnosed with: severe arterial hypertension and hypertensive emergency: blood pressure (BP) level ≥ 160/110 mmHg or hypertensive peak of any value, associated with symptoms or signs of target organ lesion; severe preeclampsia: BP ≥ 160/110 mmHg and/or symptomatology of target organ compromise and/or proteinuria determined by dipstick ++ or over 24 hours ≥ 2g; and/or oliguria < 30 ml/hour and/or thrombocytopenia < 100.000 mm3; eclampsia: presence of seizures in a preeclamptic woman; and HELLP syndrome: presence of at least one parameter: LDH ≥600U/L; bilirubin ≥1.2mg/dl; AST ≥70U/L; or thrombocytopenia < 100.000 mm3.[18,20] The cases were classified according to the WHO criteria into PLTC, NM/MD [15]. The study was approved by the local IRB and by the National Human Research Ethics Committee, under the letter of approval 097/2009.

The variables studied were: sociodemographic characteristics, obstetric history, history of previous disease, patient access to obstetric care, mode of delivery, perinatal results, clinical complications and advanced life support interventions (excluding all

those already defined as near miss criteria[15]), in addition to identification of the "three delays" according to the model originally developed by Taddeus and Maine.[21]

Bivariate analysis was performed to identify factors associated with outcomes by estimating prevalence ratios (PR) and their respective 95% confidence intervals (CI), adjusted for cluster effect (maternity hospitals or centres). Finally, Poisson multiple regression analysis was performed, also adjusted by cluster. A 95% confidence level was used (with a 5% level of significance) and the software used for analyses were SPSS® version 17 (SPSS, Chicago, IL, USA) and Stata® version 7.0 (StataCorp, College Station, TX, USA).

Results

In the one-year study period, there were 82.144 live births (LB) in the 27 maternity hospitals participating in the study and 9555 women received a diagnosis of SMM. Severe HD were associated with 70% of these hospital admissions (6706/9555), corresponding to 81.6 cases per 1000 deliveries. Among the total number of women with severe HD, 94% were classified as PLTC (6315/6706), while 349 cases had organ dysfunction or failure, with an incidence of 4.2 NM cases per 1000 LB, and a mortality index of 10.7% (42 MD per 391 cases of NM plus MD), the case/fatality rate was 8.3 NM cases to 1 MD (Table 1).

Table 2 highlights the percentage of approximately 20% of adolescents with SMM due to severe HD, without any significant association with maternal outcome. Age older than 40 years increased the risk of NM or MD by almost twice (PR_{adj} 1.67; IC 1.21 – 2.31), which was not confirmed by regression analysis. The risk of NM or MD decreased about 40% in women self-reported as non-white and in those without a steady partner on hospital admission, but these findings were not confirmed in the multivariate analysis. Maternal history of some chronic diseases such as kidney disease (PR_{adj} 4.17; 2.49 – 6.98), connective tissue disorders (PR_{adj} 4.30; 2.16 – 8.56) and heart diseases (PR_{adj} 4.09; 2.18 – 7.64) increased around fourfold the risk of NM/MD. The prevalence of chronic arterial hypertension was 30% and of diabetes was 3% in the total number of women with severe HD without significant association with the outcome. History of heart disease was independently associated with a worse outcome by regression analysis (PR_{adj} 1.98; 1.19 – 3.29).

During pregnancy and at the time of hospital admission, healthcare insurance was mainly provided by the national public healthcare system (SUS) and this was not associated with maternal outcome. Furthermore, the adequacy of prenatal care, evaluated by the number of visits for each gestational age, was appropriate in more than 70% of the total number of cases, with no association with NM/MD. Lower gestational age (GA) at the time of hospital admission due to severe HD (early manifestation of disease) and also postpartum admission were strongly associated with worse outcome. In addition, women with NM and MD had about twice the rate of elective Caesarean sections. Emergency access to an obstetric referral centre by ambulance, even in a scheduled transference was two to three times higher in the NM and MD group; the diagnosis of NM already existed in around 30% of cases at the time of patient admission to study maternity hospitals (data not shown in table). Most women with severe HD suffered some kind of delay in receiving care (55.6%) and these went to the second type, i.e. related to the healthcare system (PRadj 2.86; 1.89 – 4.33) and third type, those related to healthcare professionals (PRadj 2.45; 1.53 – 3.92) (Table 3).

Table 4 shows maternal complications (haemorrhagic conditions e.g. placental abruption, postpartum haemorrhage, and clinical conditions, such as acute pulmonary edema) and perinatal outcomes associated with NM and MD cases. There was also a more frequent need for advanced care such as blood transfusion and admission to ICU. Magnesium sulphate was used in a little more than half the total number of cases (68.4%) and showed no significant difference among groups. For analysis of clinical complications or advanced care procedures associated or not with maternal outcome, it is worth mentioning that all conditions already defined by WHO as near miss criteria (clinical, laboratory or management) were excluded. Perinatal outcome was unfavourable, especially among NM/MD cases, with 13% of anoxic newborns, almost 70% with low birth weight and more than 40% were hospitalized. Perinatal mortality was 6.6%, with 21.9% versus 5.7% among women with NM/MD compared to those with PLTC, respectively.

In Table 5, Poisson multiple regression analysis identified variables independently associated with NM and MD cases: history of heart disease, acute pulmonary edema, postpartum haemorrhage and early manifestation of disease in relation to gestational age, or hypertension remote from term. Blood product transfusion, admission to ICU, invasive mechanical ventilation non-related to anaesthesia and longer periods of

hospitalization were highlighted as significant management procedures associated with worse outcome. Delays in obtaining adequate obstetric care were also identified by difficulties linked to healthcare services and health professionals.

Discussion

In this study, we applied the Near Miss criteria according to WHO recommendation[15] to a group of women with severe hypertensive disorders, following clinical diagnoses of severe preeclampsia, eclampsia, HELLP syndrome and severe arterial hypertension/ hypertensive emergency, justified by a greater specificity of these criteria to case severity. Therefore, the capacity to identify clinical, obstetric and/or epidemiological markers for organ dysfunction and/or failure was increased in this group of women. We also performed the analysis of delays after a systematic evaluation of data collected for interventions that are beneficial to a reduction in morbidity and mortality due to hypertension,[22,23] such as the use of magnesium sulphate and the collection of variables related to obstetric care, such as patient access to referral centres, among others.

To increase the likelihood of identifying NM/MD markers in this group of women, we conducted a multicentre study in 27 referral maternity hospitals. Most of these hospitals were public and rendered service by the national healthcare system (SUS). These maternity hospitals were distributed in the five Brazilian regions and had at least 1000 deliveries per year. With a prospective surveillance system for identifying cases of severe maternal morbidity admitted to hospital, it was possible to collect data on all women and select those hospitalized due to severe hypertensive disorder for this study. Our results showed a rate of 81.6 SMM cases of severe hypertensive disorders per 1000 LB. These numbers create demand for hospital beds specialized in the management of these conditions and corroborate the high prevalence of complications that result in hospitalizations due to hypertensive disorders in general.[2,3.]

With this method, we identified an incidence of 4.2 NM cases due to severe HD per 1000 LB and the case/fatality rate was 8.3 cases to 1 death, or 349 NM: 42 MD (considering the number of NM cases for the numerator) and mortality index of 12%, when evaluated for the number of deaths by the total number of NM (42MD/349NM). This was much higher than those found in high-income countries, which was 0 to 1.8%[24-26] and in

intermediate to low-income countries (0.5 to 20.7%) [12,27-30]. It is noteworthy that studies in high-income countries used clinical criteria for the diagnosis of NM (severe preeclampsia, eclampsia and HELLP syndrome). Studies of low-income countries selected cases of organ dysfunction and/or failure among clinical diagnoses and therefore used a method similar to ours. In this study, a high ratio of specific maternal mortality due to HD was found, with 51 deaths per 100.000 LB in these maternity hospitals.

Among the maternal sociodemographic, obstetric, and clinical variables, older maternal age was identified as a risk factor for worse outcome, a finding that is in agreement with results in the literature.[31] Some comorbid conditions that are relevant in studies investigating severe maternal morbidity are also associated with a worse outcome, not only for the hypertensive disorder group.[31] Contrary to what has been reported in the literature, non-white colour, marital status and living with a steady partner were variables associated with a lower risk of NM/MD. Although the same findings were not confirmed in the multivariate analysis, these results were quite surprising. Anyway there are some arguments that could possibly explain them: in Brazil, racial miscegenation is high and race was dichotomously categorized as white or non-white, which may have contributed to reduce differences between groups. Regarding marital status however we found no answers and only identified in the literature a qualitative study conducted in a low-income country reporting a negative influence of partner and family members on the woman's decision to seek medical care when she perceived symptoms.[32] On multivariate analysis, these variables did not show to be associated with outcome. It is also important to consider that all women included in the study already had a severe clinical picture, and this condition may have contributed to a greater homogeneity between groups.

Among the obstetric variables, the most noteworthy is early manifestation of hypertensive disease, evaluated by the lowest gestational age at the time of admission. This condition is recognized in the specific literature as a predictor of poor maternal and perinatal prognosis.[18,33,34] There is also an increased potential for the presence of subclinical disease, such as systemic lupus erythematous, kidney or thrombotic disease.[34-37] This condition remained an independent variable for worse maternal outcome by multivariate analysis and was confirmed as a marker of poor maternal and perinatal prognosis, reinforcing recommendations of early admission to tertiary or referral centres, for adequate

management of the woman and fetus. In addition, assessment of the best time for therapeutic delivery is warranted, since it also results in a higher incidence of preterm birth and thus increased need for neonatal intensive care therapy. In this study, preterm occurred in more than 40% of the total number of newborn infants and the incidence was higher in the NM/MD group. This poor perinatal outcome was in agreement with a population-based study on the impact of hypertensive disorders in perinatal mortality. [38]

Among the clinical maternal variables identified by Poisson multiple regression analysis, a history of heart disease remained significantly associated with a worse maternal prognosis. Research studies conducted with pulmonary artery catheterization showed that women suffering from chronic arterial hypertension with superimposed preeclampsia had a higher risk of developing pulmonary [39] edema and also heart failure. Sibai suggested that women with chronic arterial hypertension be evaluated in the preconception period or at the beginning of pregnancy for the presence of target organ (heart, kidneys) damage. These cases are termed "high-risk" and prenatal care should be specialized to minimize maternal/perinatal morbidity and mortality.[40] Chronic arterial hypertension was the major comorbid condition identified in around one-fourth of the cases with severe HD.

Acute pulmonary edema is also a clinical marker of cardiopulmonary complication. The pathophysiology of preeclampsia favours the occurrence of this condition. Fluid overload imposed on these women may increase the incidence of pulmonary edema, especially during anaesthetic procedures and in the postpartum period [41] and that is why fluid restriction is recommended (60 to 125 ml per hour in 24 hours) in the management of severe preeclampsia.[42] In our study, acute pulmonary edema was prevalent in 1.7% of the total number of cases. Of these, it occurred in 16.6% of the NM/MD group, while in only 0.8% among patients with PLTC. Acute pulmonary edema has already been elected an indicator for quality assessment of obstetric care in this group of women. [43]

Regarding obstetric care, it is well-known that severe hypertensive disorders, particularly eclampsia and hypertensive emergency, predispose patients to the occurrence of haemorrhagic or ischemic cerebral events, due to endothelial dysfunction associated with the loss of cerebral blood flow auto regulation that occurs in the presence of eclamptic seizure or an abrupt elevation of arterial blood pressure levels. In the United Kingdom, a study on the incidence of eclampsia and its complications reported a significant decrease

in both conditions between 1992 and 2005, after the introduction of magnesium sulphate for the management of preeclampsia and eclampsia, with no maternal death in 2005.[44] We did not classify the clinical forms of hypertension and therefore we could not evaluate the use of magnesium sulphate in these cases.

Considering obstetric complications, there is a classic association between severe hypertensive disorders and placental abruption. However, there is no distinction in the occurrence of postpartum haemorrhage. In our study this complication was present in 4% of the total number of cases, with 19% in the NM/MD group and 3% in the group with PLTC. We believe that placental abruption may represent an intermediate variable for the occurrence of postpartum haemorrhage, due to atony or uterine apoplexy, which may also lead to an increased rate of postpartum hysterectomy due to bleeding. However, this affirmation could not be made because the association between cases of placental abruption and uterine atony was not analysed. Studies have shown that the use of magnesium sulphate in the antepartum care of these cases decreases the occurrence of placental abruption[6, 45,] and may reduce this morbid condition as well.

The need for interventions to manage severe disease occurred in about 80% of these cases, with a clear predominance in the NM/MD group. Among them, mechanical ventilation, blood product transfusion, admission in intensive care units and also a longer period of hospitalization were significantly associated with a worse prognosis. These findings are in agreement with other national studies [46-48] and reinforce the need for obstetric intensive care units for patient management.

Some delays for adequate obstetric care occurred in more than half of the cases and in even a larger proportion of NM/MD cases. Factors related to healthcare system and services (second delay) and health professionals (third delay) were associated with the worst outcomes. These results unveil a fragmented care network, inefficient offices for regulation of obstetric beds and/or lack of hospital beds for the management of complex cases (obstetric intensive care units) and also a model of care that disrespects scientific evidence on what is beneficial for the treatment of hypertension, also evaluated by the use of magnesium sulfate with a prevalence lower than 70% for the total number of severe cases. These findings are in agreement with publications about barriers against the reduction in MD from hypertension, in low or middle-income countries. [8,22,43]

This study has various limitations. First, it was not a population-based study, although it had representativeness in maternity hospitals in every region of the country. Second, we did not classify the clinical forms of severe hypertension, a fact that could allow us to identify NM/MD by specific diagnosis, such as eclampsia which is recognized as the major cause of maternal morbidity and mortality in low-income and middle-income countries. [1,6,9] Classification of hypertension could also assess management with magnesium sulphate in specific clinical situations, since we believe that there was a low prevalence of magnesium sulphate use (68%), considering that all cases were severe. This finding was similar to the results of another study on the prediction of adverse outcome in preeclampsia, in which the prevalence of magnesium sulphate use was only 62%. [33] Third, we failed to explore some relevant NM aspects by patient interview, due to technical difficulties in obtaining a written informed consent term from all women regardless of clinical condition presented at the time of hospital admission. Nevertheless, it was possible to perform analysis of the delays.

On the other hand, the merit of the study is its large number of cases and the prospective surveillance using standardized definitions recently adopted and recommended by WHO. Poisson multiple regression analysis could be performed in about 5500 cases to identify and/or confirm clinical and obstetric markers independently associated with worse maternal outcome, such as hypertension remote from term, postpartum haemorrhage, history of heart disease and pulmonary edema, which may be modified by direct intervention in patient care. Furthermore, unpublished research of the delays identified weaknesses in the national healthcare system, since technical, political and administrative interventions may modify this outcome. Finally, this was the first study to address NM as defined by the WHO related to HD and reveal the possibility of implementing a prospective, hospital-based and national surveillance system for the investigation of NM, particularly in hypertension which is still the leading cause of maternal death in Brazil.

Disclosure of interests

The authors declare that there are no conflicts of interests

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Contribution to authorship

The idea for the study and this specific analytic approach arose in a group discussion among all the authors. The analyses were planned and performed by EAZ, MAP, JGC and MHS. The first version of the manuscript was drafted by EAZ and MAP, and then complemented with suggestions of all the others and mainly of FGS, MLC, SMH and JLPS. All authors contributed to the development of the study protocol and approved the final version of the manuscript.

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Ethical details

The research protocol was approved by the Institutional Review Board of the coordinating institution on 5th May 2009 (Document CEP 027/2009).

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Table 1. Women with severe hypertensive disorders (HD) among those with severe maternal morbidity or death

Condition	PLTC n (%)	NM n (%)	MD n (%)	Total n (%)
HD	6315 (73)	349 (45)	42 (30)	6706 (70)
No HD	2330 (27)	421 (55)	98 (70)	2849 (30)
Total	8645 (100)	770 (100)	140 (100)	9555 (100)

Live births = 82,144;
PLTC – Potentially life-threatening condition; NM – near miss; MD – maternal death.
MNM incidence ratio = 4.2 NM/1000LB
Severe Maternal Outcome Ratio (SMOR) = 4.75/1000LB
Maternal near miss: Maternal death ratio = 8.3NM:1MD
Mortality index = 42MD/391 = 10.7%
MMR= 51.1/100.000 LB

Table 2. Estimated risk of worse outcome among women with severe hypertensive disorders during pregnancy according to maternal characteristics, obstetric and medical history

Characteristics	%	NM+MD		PLTC		PRadj	95%CI
	Total	n	%	n	%		
Age (years)							
≤ 19	18.7	65	16.6	1186	18.8	0.98	0.77 – 1.25
20 – 29	46.9	167	42.7	2976	47.1	(ref)	
30 – 39	29.6	130	33.2	1856	29.4	1.23	0.98 – 1.55
≥ 40	4.9	29	7.4	297	4.7	**1.67**	**1.21 – 2.31**
Skin colour (a)							
white	36.3	136	46.4	1623	35.7	(ref)	
non white	63.7	157	53.6	2927	64.3	**0.66**	**0.48 – 0.91**
Education (b)							
elementary	46.0	128	51.2	2162	45.7	**1.23**	**0.88 – 1.73**
> elementary	54.0	122	48.8	2566	54.3	(ref)	
Marital status (c)							
with partner	52.7	207	67.6	2783	51.8	(ref)	
without	47.3	99	32.4	2589	48.2	**0.53**	**0.37 – 0.76**
Gestation N (d)							
1	45.7	159	41.4	2893	45.9	0.91	0.72 – 1.16
2 - 3	37.0	141	36.7	2330	37.0	(ref)	
4 or more	17.4	84	21.9	1076	17.1	1.27	1.00 – 1.61
Childbirth (d)							
0	52.4	178	46.4	3327	52.8	0.80	0.65 – 1.00
1 - 2	36.3	153	39.8	2270	36.0	(ref)	
3 or more	11.3	53	13.8	702	11.1	1.11	0.76 – 1.63
Previous C- section (e)							
0	76.8	282	75.0	4797	76.9	(ref)	
1 or more	23.2	94	25.0	1442	23.1	1.10	0.86 – 1.41
Medical history (f)							
chronic hypertension	22.9	92	28.0	1243	22,6	1.30	1.00 – 1.70
diabetes	2.7	16	4.9	139	2.5	1.87	1.00 – 3.49
kidney disease	1.3	17	5.2	58	1.1	**4.17**	**2.49 – 6.98**
collagen disorders	0.4	6	1.8	19	0.3	**4.30**	**2.16 – 8.56**
heart disease	1.5	19	5.8	67	1.2	**4.09**	**2.18 – 7.64**
smoking	3.5	12	3.6	194	3.5	1.03	0.50 – 2.11
Total		391		6315			

PRadj: prevalence ratio adjusted by cluster
Missing data: (a) 1863 cases; (b) 1728 cases; (c) 1028 cases; (d) 23 cases; (e) 91 cases; (f) 888 cases

Table 3. Estimated risk of worse outcome among women with severe hypertensive disorders during pregnancy according to characteristics of current pregnancy and delays in obstetric care

Characteristics	Total	NM + MM		PLTC		PRadj	95%CI
	%	n	%	n	%		
PN coverage (a)							
Public	92.7	291	90.7	4566	92.6	0.76	0.47 – 1.23
Other	7.3	30	9.3	351	7.1	(ref)	
PN adequacy (b)							
No	23.6	84	21.9	1486	23.7	0.91	0.71 – 1.15
Yes	76.4	299	78.1	4771	76.3	(ref)	
Hospitalization coverage (c)							
Public	99.3	386	98.7	6269	99.4	0.53	0.17 – 1.66
Other	0.7	5	1.3	41	0.6	(ref)	
GA at hospitalization (d)							
<22	1,5	12	3.1	86	1.4	**5.06**	**2.60 – 9.82**
22 – 27	4.9	35		288	4.6	**4.47**	**2.53 – 7.92**
28 – 33	20.7	111	28.9	1265	20.2	**3.33**	**2.21 – 5.02**
34 – 36	22.5	89	23.2	1409	22.5	**2.45**	**1.59 – 3.79**
≥37	47.2	76	19.8	3062	48.9	(ref)	
Postpartum	3.2	61	15.9	152	2.4	**11.82**	**7.59 – 18.43**
GA at delivery (e)							
<22	0.5	3	0.9	30	0.5	**3.23**	**1.13 – 9.28**
22 – 27	3.0	27	7.8	172	2.8	**4.83**	**2.72 – 8.57**
28 – 33	17.5	110	31.8	1030	16.7	**3.43**	**2.19 – 5.38**
34 – 36	22.6	96	27.7	1380	22.3	**2.31**	**1.57 – 3.41**
≥37	51.8	95	27.5	3284	53.1	(ref)	
still pregnant	4.6	15	4.3	284	4.6	**1.78**	**1.03 – 3.10**
Mode of delivery (f)							
C-section	74.8	309	79.8	4694	74.5	1.33	0.99 – 1.79
other	25.2	78	20.2	1605	25.5	(ref)	
Onset of labor (g)							
spontaneous	26.8	66	17.7	1716	27.4	(ref)	
induction	9.0	33	8.9	562	9.0	1.50	0.86 – 2.60
elective C-section	59.0	254	68.3	3665	58.5	**1.75**	**1.11 – 2.76**
abortion	0.6	4	1.1	37	0.6	**2.63**	**1.05 – 6.59**
still pregnant	4.5	15	4.0	285	4.5	1.35	0.77 – 2.37
Access to referral center (h)							
not scheduled	10.2	69	18.4	576	9.7	**2.98**	**1.62 – 5.47**
scheduled	46.4	207	55.3	2715	45.9	**1.97**	**1.30 -2.97**
spontaneous	43.3	98	26.2	2628	44.4	(ref)	
Delays							
Women/family members (i)	39.9	146	44.9	2179	39.6	1.23	0.89 – 1.69
Health service (j)	16.2	129	35.6	874	15.0	**2.86**	**1.89 – 4.33**
Health professional (l)	19.1	132	36.6	1066	18.0	**2.45**	**1.53 – 3.92**
Any delays	55.6	256	73.6	3131	54.5	**2.22**	**1.44 – 3.43**
Total		391	100	6315	100		

PRadj= prevalence ratio adjusted by cluster
Missing data: (a)1468 cases; (b) 66 cases; (c) 5 cases; (d) 60 cases; (e) 180 cases; (f) 20 cases; (g) 69 cases; (h) 413; (i) 875 cases; (j) 513 cases; (l) 613 cases

Table 4. Maternal complications and perinatal results of current pregnancy associated with worse outcomes

	%	NM + MD		PLTC			
	Total	**n**	**%**	**n**	**%**		
Pregnancy outcome*							
placental abruption	3.6	37	9.5	207	3.3		
postpartum hemorrhage	4.0	74	18.9	196	3.1		
other severe hemorrhage	0.5	17	4.3	19	0.3		
pulmonary edema	1.7	65	16.6	48	0.8		
Thromboembolism	0.2	2	0.5	9	0.1		
Sepsis	1.0	49	12.5	15	0.2		
Advanced life-support procedures *	79.4	384	98.2	4938	78.2		
blood transfusion	7.9	207	52.9	326	5.2		
ICU admission	21.9	290	74.2	1178	18.7		
Hospital stay >7days	30.7	253	64.7	1805	28.6		
invasive mechanical ventilation	1.8	116	29.7	2	0.0		
magnesium sulphate use	68.4	279	71.4	4309	68.2		
						PRadj	**95% CI**
Perinatal results							
Apgar at 5 min < 7 (a)	3.3	34	12.9	164	2.9	**4.28**	**3.26 – 7.38**
Apgar at 5 min ≥7	96.7	230	87.1	5505	97.1	(ref)	
birth weight <2500g (b)	42.3	212	68.6	2388	40.9	**2.98**	**2.10 – 4.22**
birth weight ≥2500g	57.7	97	31.4	3447	59.1	(ref)	
stillbirth (c)	4.2	60	17.7	203	3.4	**4.90**	**3.26 – 7.38**
live birth	95.8	279	82.3	5715	96.6	(ref)	
Neonatal Outcome (d)							
neonatal death	2.4	11	4.2	124	2.3	**2.50**	**1.35 – 4.60**
ICU admission	22.3	107	41.3	1172	21.4	**2.56**	**1.53 – 4.28**
hospital discharge	75.3	141	54.4	4179	76.3	(ref)	
Total		391	100	6315	100		

* excluded all near miss criteria according to WHO
PRadj: prevalence ratio adjusted by cluster
Missing data: (a) = 773 cases; (b) = 562 cases; (c) = 449 cases; (d) = 972 cases.

Table 5. Multivariate analyses with variables independently associated with worse maternal outcome (N = 5488)

Variables	PRadj	95% CI	p
Clinical			
GA <37 weeks or postpartum at hospital admission	1.73	1.22 – 2.44	0.003
Postpartum hemorrhage	1.60	1.28 – 2.00	<0.001
Pulmonary edema	1.86	1.24 – 2.82	0.005
Previous heart disease	1.98	1.19 – 1.59	0.029
Management			
Blood transfusion	3.67	2.48 – 5.44	<0.001
Invasive mechanical ventilation	2.83	1.99 – 4.01	<0.001
ICU admission	3.75	2.06 – 6.82	<0.001
Hospital stay >7days	1.66	1.18 – 2.33	0.005
Delay			
health system	1.60	1.19 – 3.29	0.010
health professional	1.28	1.03 – 1.59	0.029

PRadj = prevalence ratio adjusted by cluster and all other predictors entering the model

5. Conclusões

– Os DH graves foram a principal causa de morbidade materna grave ou 70% do total (6706/9555), correspondendo a 81,6 casos por 1000 NV e a prevalência/incidência de NM foi 4,2 casos por 1000 NV.

– Encontraram-se os seguintes indicadores do cuidado obstétrico: RMM = 51/100.000 NV; desfecho materno grave = 4,75/1000 NV; relação NMM: MM (caso/fatalidade) = 8,3 casos NM: 1 MM; índice de mortalidade (IM%) = 10,7%.

– A idade materna ≥ 40 anos e os antecedentes de doença renal, colagenose e cardiopatia elevaram de duas a quatro vezes o risco para NM/MM. A cor não branca e viver sem companheiro reduziu o risco para NM/MM. Apenas o antecedente de cardiopatia manteve-se independentemente associado ao desfecho em NM/MM.

– A menor IG na admissão, na resolução da gravidez ou a internação no pós-parto estiveram fortemente associadas ao desfecho para NM/MM. A cesariana eletiva foi mais frequente neste grupo. O acesso da mulher à maternidade,

por transferência programada ou não programada, aumentou em duas a três vezes o risco para NM/MM, comparada aquelas com acesso espontâneo. A maioria das mulheres sofreu algum tipo de demora (55,6%) e 73% delas ocorrerram no grupo de NM/MM, sendo relacionadas ao serviço/sistema de saúde e aos profissionais de saúde. Na análise múltipla, a menor idade gestacional ao diagnóstico da doença e as demoras mantiveram-se significativamente associadas ao pior desfecho materno.

– Excluindo os critérios definidos como near miss pela OMS, as complicações clínicas (edema agudo de pulmão) e obstétricas (hemorragia pós-parto) estiveram independentemente associadas ao desfecho materno em NM/MM. Cerca de 80% dos DH graves tiveram algum manejo de gravidade (transfusão hemoderivados, ventilação mecânica invasiva, internação em UTI). A prematuridade ocorreu em quase metade dos casos com DH graves. No grupo com NM e MM, cerca de 70% dos RN tiveram peso menor que 2.500 gramas, 13% com Apgar de 5º minuto < 7 e mais de 40% permaneceram internados.

– Nas mulheres com DH graves, o sulfato de magnésio foi utilizado em 68% do total de casos.

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7. Anexos

7.1. Anexo 1 – Parecer do Comitê de Ética em Pesquisa

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 nestas 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

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.

VII- 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

7.2. Anexo 2 – Artigo sobre a criação da Rede Brasileira de Vigilância de Morbidade Materna Grave

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From planning to practice: building the national network for the surveillance of severe maternal morbidity

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Abstract

Background: Improving maternal health is one of the Millennium Development Goals for 2015. Recently some progress has been achieved in reducing mortality. On the other hand, in developed regions, maternal death is a relatively rare event compared to the number of cases of morbidity; hence studying maternal morbidity has become more relevant. Electronic surveillance systems may improve research by facilitating complete data reporting and reducing the time required for data collection and analysis. Therefore the purpose of this study was to describe the methods used in elaborating and implementing the National Network for the Surveillance of Severe Maternal Morbidity in Brazil.

Methods: The project consisted of a multicenter, cross-sectional study for the surveillance of severe maternal morbidity including near-miss, in Brazil.

Results: Following the development of a conceptual framework, centers were selected for inclusion in the network, consensus meetings were held among the centers, an electronic data collection system was identified, specific software and hardware tools were developed, research material was prepared, and the implementation process was initiated and analyzed.

Conclusion: The conceptual framework developed for this network was based on the experience acquired in various studies carried out in the area over recent years and encompasses maternal and perinatal health. It is innovative especially in the context of a developing country. The implementation of the project represents the first step towards this planned management. The system online elaborated for this surveillance network may be used in further studies in reproductive and perinatal health.

Keywords: surveillance network severe maternal morbidity, near-miss, multicenter cross-sectional study

Background

The reduction of maternal mortality is one of the targets of the Millennium Development Goals for 2015 [1]. In some countries, some progress has been achieved, but there is very little progress in the most of high mortality countries [2-4].

The high mortality ratios result mainly from difficulties in accessing healthcare services, the inadequate management of obstetrical complications and failure to provide effective interventions in poorly developed areas [5]. On the other hand, the occurrence of maternal death in developed settings is a relatively rare event compared to the total number of women who survive such complications [3]. The study of severe maternal morbidity has been suggested as a useful approach to investigating quality of health care systems in order to improve women's healthcare and effectively reduce

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maternal morbidity [5]. Nevertheless, differences also exist in the definitions and procedures used to identify cases of morbidity, which need also progressive transformation and development [6,7]. Hospital-based and population-based studies have shown that lack of standardization of the criteria used to define severe maternal morbidity, difficulty in identifying and reporting these conditions both with official records and by the women themselves, and the limitations of retrospectively conducted studies [8-14].

Electronic surveillance systems may introduce improvements in the process by facilitating complete data reporting and reducing the time required for data collection and analysis [15-18]. With the objective of providing support for healthcare programs, epidemiological surveillance systems may be defined as "the ongoing and systematic collection, analysis and interpretation of health data in the process of describing and monitoring a health event" [19]. In improving healthcare, greater benefits are obtained when an integrated system of data technology is available and if this systematic electronic data capture system is associated with a program to identify risks and propose clinical management based on evidence [20]. Few countries and institutions have well-structured systems of health data technology in which data are used in real-time for adjusting healthcare and performing surveillance [21-25].

Even in places where the health surveillance system is adequately structured such as in Canada, severe maternal morbidity is not yet fully studied due to various factors: the need to standardize the concepts, the range of the area in which surveillance has to be carried out and the prospective individual evaluation of each identified case, with effective feedback conveyed to the healthcare providers [25].

In Brazil, the distribution of maternal death is associated with disparities in socioeconomic development. Brazil's large territorial extension is also associated with cultural differences and socioeconomic inequalities, resulting in heterogeneity with respect to the incidence of complications and in the ways of dealing with them [26]. Health-related data systems are almost exclusively used for epidemiological evaluation and global management, and are not integrated into a specific prospective evaluation of care.

Only a few initiatives for the surveillance of maternal mortality and severe maternal morbidity have been carried out prospectively [23,24]. As recently defined by the WHO, maternal near-miss refers to a situation in which a woman almost dies but survives a life-threatening complication of pregnancy, childbirth or in the first 42 days following delivery [5]. In order to facilitate the practical use of this concept, potentially life-threatening conditions were listed that, together with specific criteria defining maternal near-miss, would operationally characterize the broader concept of severe maternal morbidity.

As a result, the surveillance and proposal of strategies to reduce maternal deaths worldwide may be founded on a single conceptual basis. Therefore, the objective of the present manuscript was to describe the methods and procedures adopted for the creation and implementation of the National Network for Surveillance of Severe Maternal Morbidity in Brazil [27], covering all the regions of the country and using the new standardized criteria for maternal near miss recently defined by the WHO [5].

Methods

Protocol design

In 2002, research was initiated at the University of Campinas, Brazil, focusing on severe maternal morbidity. The transition from studying death to studying maternal morbidity followed a worldwide trend, considering the absolute number of deaths is relatively small compared to the number of cases of morbidity. Data on maternal morbidity are more accessible and reliable for the evaluation of quality in obstetrical care. Within this scope, a study was conducted to evaluate the applicability of different concepts of severe maternal morbidity and of a severity score to identify cases of maternal morbidity [9].

Elaborating further on the concept that routine health data would be useful for systematically identifying the occurrence of complications associated with pregnancy, the National Health Service's Hospital Information System was evaluated. Data routinely collected from medical records of women with conditions suggestive of severe maternal morbidity were selected, and the diagnoses and procedures used in such cases were described in order to identify factors associated with the occurrence of maternal death [15]. Next, further evaluations on maternal morbidity were performed using data from demographic health surveys. The importance of the use of validated questionnaires for obtaining information on morbidity and the regional differences in the prevalence of morbidity were also highlighted [11].

Considering that the early identification of cases of maternal morbidity would allow a more appropriate way of monitoring, managing and preventing deaths [28], the proposal to establish the National Network for Surveillance of Severe Maternal Morbidity was developed as a research proposal [27].

Organization of the project

The project is a multicenter, cross-sectional study to be implemented in referral obstetrical units in all geographical regions of Brazil. Over a 12-month period,

prospective surveillance and data collection was planned to be performed to identify cases of maternal near-miss and potentially life-threatening conditions in accordance with the new criteria defined by WHO [5].

To determine the number of collaborating centers to be included in the study, sample size was calculated according to the number of deliveries that would have to be covered to identify cases of near-miss. Based on a previously reported incidence of 8 cases for 1000 deliveries [9], approximately 70,000 deliveries would have to be monitored. This number was believed to be sufficient to validate the new criteria issued by WHO [5]. The study population is composed of all the women admitted to the participating hospitals during the study period who suffer organ dysfunction (that will be a near-miss case or a maternal death, Table 1) or presenting potentially life-threatening conditions (Table 2), who die or are transferred to other healthcare services because they require more specialized services or procedures.

During the data collection period, at each participating hospital, local coordinators perform a daily review of all admitted women, looking for cases with any of the conditions indicative of severity (Table 2). The lists of patients with these diagnoses are sent for review and data collection following the patient's discharge from hospital, death or transfer to another hospital. Data unavailable from the record is obtained from the attending team. Data are collected on demographic and obstetrical characteristics, primary determinant of severe morbidity (the first complication in the chain of events that led to severe maternal morbidity), length of hospitalization, occurrence of any criteria of maternal near-miss, perinatal outcome and condition of the woman at discharge from hospital. The data are collected on a pre-coded form and are then sent electronically to the database. The manually completed forms are filed in such a way as to be easily accessible for inspection during technical quality control visits.

Table 1 Potentially life-threatening maternal conditions

HEMORRHAGIC COMPLICATIONS	
Abruptio placentae	Postpartum hemorrhage
Placenta previa/accreta/increta/percreta	Atony
Ectopic pregnancy	Retained placenta
Ruptured uterus	Perineal lacerations
Severe hemorrhage due to abortion	Coagulopathy
	Uterine inversion
HYPERTENSIVE DISORDERS	
Severe preeclampsia	Severe hypertension
Eclampsia	HELLP syndrome
Hypertensive encephalopathy	Acute fatty liver of pregnancy
OTHER COMPLICATIONS	
Pulmonary edema	Acute respiratory failure
Seizures	Acidosis
Sepsis	Cardiopathy
Postpartum endometritis	Cerebrovascular accident
Post abortion endometritis	Coagulation disorders
Urinary infection	Thromboembolism
Chest infection	Diabetic ketoacidosis
Thrombocytopenia < 100 000 platelets	Jaundice/hepatic dysfunction
	Meningitis
Thyroid crisis	Acute renal failure
Shock	
MANAGEMENT INDICATORS OF SEVERITY	
Transfusion of blood derivatives	Intubation unrelated to anaesthesia
	Return to operating theater
Central venous access	Major surgical intervention (hysterectomy, laparotomy)
ICU admission	
Prolonged hospital stay (> 7 days)	Use of magnesium sulfate

Table 2 WHO criteria for maternal near miss[5]

CLINICAL CRITERIA	
Acute cyanosis	Loss of consciousness for ≥ 12 h
Gasping	Unconscious, no pulse/heartbeat
Breathing rate > 40 or < 6 per minute	Cerebrovascular accident
	Uncontrolled convulsions/total paralysis
Shock	
Oliguria unresponsive to fluids or diuretics	Jaundice concomitantly with preeclampsia
Coagulation disorders/clotting failure	
LABORATORY CRITERIA	
Oxygen saturation < 90% for > 60 minutes	pH < 7,1
	Lactate > 5
PaO2/FiO2 < 200 mmHg	Acute thrombocytopenia (< 50 000 platelets)
Creatinine ≥ 300 mmol/l or ≥ 3,5 mg/dL	
	Unconscious, presence of glucose and ketoacidosis in urine
Bilirubin > 100 mmol/l or ≥ 6,0 mg/dL	
MANAGEMENT CRITERIA	
Use of continuous vasoactive drug	Intubation and ventilation for a period ≥ 60 minutes, unrelated to anesthesia
Postpartum or post abortion hysterectomy due to infection or hemorrhage	Dialysis for treatment of acute renal failure
Blood transfusion ≥ 5 units of red cell	Cardiopulmonary resuscitation (CPR)

Selection of the centers to constitute the network

After the general proposal was ready, a meeting was held during a national congress of the Brazilian Federation of Societies of Gynecology and Obstetrics in November 2007 where representatives of several healthcare institutions from around the country were present. The proposal to establish a National Network for Surveillance of Severe Maternal Morbidity was presented and those interested in participating applied for that.

Before the project could be implemented, the proposal was submitted for public funding and, following approval, an invitation letter was sent to all interested institutions, together with a summary of the planned objectives and methods. In addition, a form designed to obtain information on the characteristics of the collaborating center was also sent to the local investigator.

Basically, it had information on identification and location of the institution, nature and complexity level of the hospital, population covered, number of beds in the maternity department, availability of resources for more specialized care (blood bank, obstetrical and neonatal intensive care units, specialist care for high risk pregnancies, availability of other medical or surgical specialities, ultrasonography, laboratory, anesthetists available round the clock, resources for the parenteral administration of antibiotics, oxytocin and magnesium sulphate, resources for general anesthesia, mechanical ventilation, cardiorespiratory resuscitation of adults and newborn infants, hysterectomy), number of deliveries performed annually (minimum number required above 1,000 deliveries/year), availability of broadband internet connection, data on the prevalence of some obstetrical interventions based on scientific evidence performed during delivery, and availability of written protocols of procedures in the service.

Additionally telephone contacts occurred between the principal investigator and the person responsible for the institution. As a result of these different approaches, 35 institutions from all over Brazil applied for participating in the study. Evaluation of their characteristics and geographical distribution led to the selection of 27 institutions that fulfilled all the inclusion criteria.

Review of the criteria for severe maternal morbidity and data collection forms

Following selection of the centers, a meeting was held in August 2008 with the principal investigators from each center at the project headquarters in Campinas. At this time, a term of agreement was signed by all attendants to compose a Brazilian Network for Studies in Reproductive and Perinatal Health. The objective of this alliance was to proceed to develop further studies in the future in the matter, using the same multicenter strategy of achieving regional diversity in a developing country with continental extensions. The meeting lasted for two days when the research proposal was reviewed and discussed, the concepts of near miss and severe maternal morbidity were presented, the data collection forms were structured and the concept of developing an electronic data collection system was introduced. A copy of the proposal was provided to each center, to be evaluated and approved locally. The coordinating center had the research protocol approved by the local institutional review board (Committee of Ethics in Research from the School of Medical Sciences, University of Campinas - Approval letter CEP 097/2009), and then by the national IRB.

Selection of the electronic research system

The viability of the entire project depended on approval of the request for funding submitted to the National Research Council (CNPq)/Department of Science and Technology (DECIT). Initially, the plan was to develop software and a customized data management system control system for the study. Nevertheless, due to some practical constraints, it was decided to use a system that had already been developed and that would be cheaper to maintain. Therefore, a free, open source, online data entry system was selected (OpenClinica®) [29], which is available for use in clinical trials, was selected. This internet-based system consists of an electronic platform for data entry and management of data and is designed to support all types of clinical studies in a variety of locations [29]. The system permits autonomy in creating forms, in analyzing and storing data and in stratifying the right of access to be granted to users working in the same study (Figure 1).

Results

Development of specific software and hardware tools

Following selection of an electronic data entry system for the network and registration of the study in the OpenClinica®, an internet server was created in the host institution to safely store the data. The electronic address of the server was hosted in the institution's homepage with an individual safety certificate https://openclinica.caism.unicamp.br:8443/OpenClinica/MainMenu that allowed encrypted data to be sent to the central database (Figure 1). A detailed training was then carried out for the development of an electronic environment to serve the network. For this purpose, usernames and passwords were created for all research team, allowing individual access to their respective centers. Investigators, coordinators, supervisors, data managers at central and local levels were granted different levels of accessibility and privileges for the inclusion and evaluation of data. The electronic data collection form was developed in accordance with the standardized pattern offered by the system, with the inclusion of different sections containing all the variables pertinent to the study. Several versions had to be created and evaluated internally before the final version was reached.

Development of material

In order to identify potential research subjects during hospitalization, an identification form was developed listing all the potentially life-threatening conditions. This form was produced and provided to the centers as a suggestion for use in selecting subjects at the moment of their discharge from hospital, mainly for hospitals with a large number of admissions. The manual data collection form was developed with exactly the same structure as the electronic version.

The manual of operations was designed to contain all the information required by the investigators and to provide well-structured material that could be easily and rapidly accessed. It contains the main concepts of the

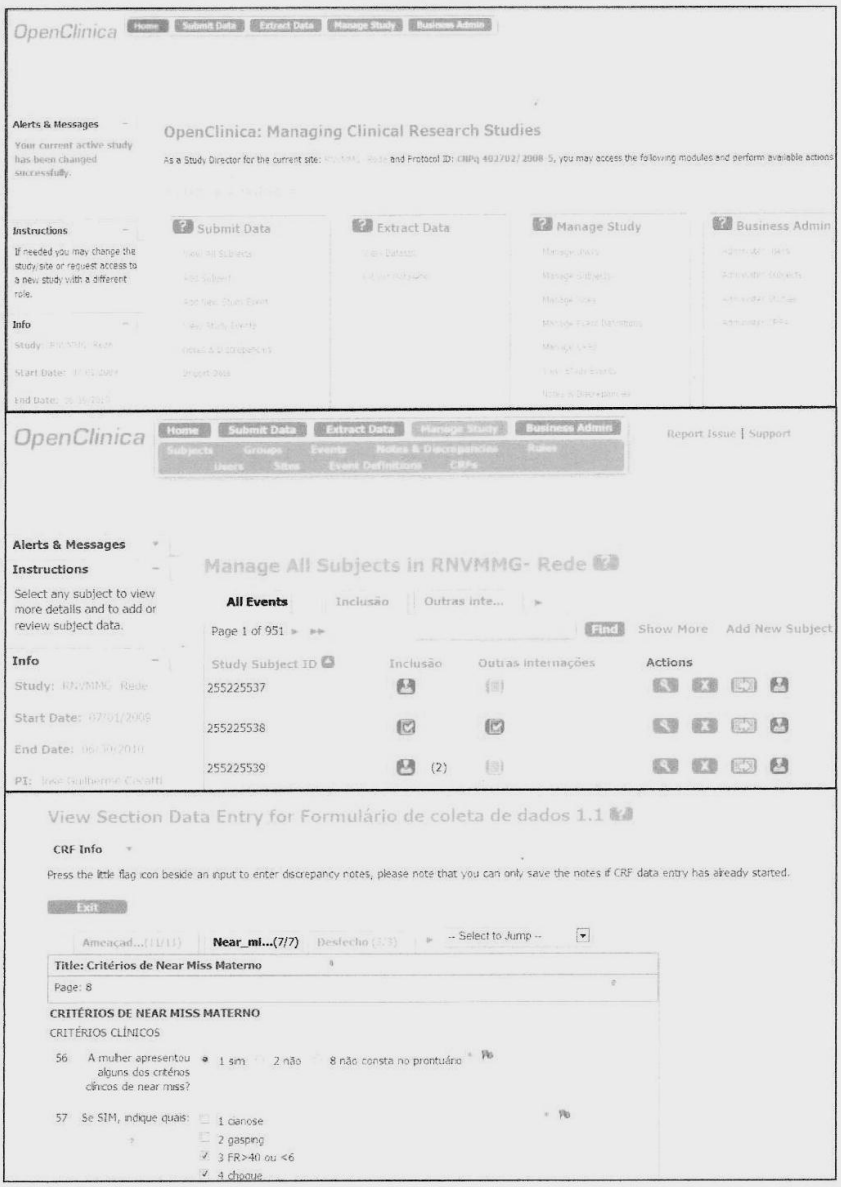

Figure 1 Sample screens from the online data entry and management system: A. Cover sheet for the study in OpenClinica; B. Form for the management of all subjects; C. Form for data entry on criteria for maternal near-miss.

study, information on the participating centers and investigators, a detailed description of the basic steps involved in electronic data input and management and standardized definitions of the variables used in the study.

Implementation process

With electronic data system and preliminary materials ready, a meeting was held in Campinas in April 2009 to present the system to all research teams and train them to use the the network. To assure the minimal material infrastructure required for the study, a computer was supplied to each center and training was provided using these same computers in an appropriate environment with internet support. The study documents and procedures were presented at the meeting and distributed to all the participants, who then discussed them and the

electronic data system, making suggestions for changes in accordance with their individual experience at each site. The material was tested and personnel trained in its use through the presentation of clinical cases of maternal morbidity and mortality in order to recreate situations as close as possible to the actual routine expected for the study.

The meeting lasted three days and, in addition to practical training in the system, operational procedures were discussed to ensure that the study would function homogenously in the different sites of the network. It provided the opportunity to deal with a variety of aspects including defining concepts, routine procedures and the way the centers would operate. These debates resulted in changes that improved the instruments and standardized network operations.

Data collection was planned to start simultaneously in all centers, which happened at the beginning of July, 2009. The forms and manual of operations were provided to the investigators on a password-protected virtual disk, which is also hosted at the website, and contains the latest versions of all the documents used in the network.

Analysis of the implementation process

After data collection was initiated, the process of data consistency checks and technical visits to the participating centers also started. Communication between all centers and the coordinating center was generally conducted by e-mail and telephone contact was seldom required. To verify the consistency of cases included in the system, a schedule was developed to be carried out at each individual center. During this procedure, all included cases are checked for inconsistencies by a team of trained research assistants in the coordinating center following a pretested protocol of general and specific consistencies between variables. Any errors or queries identified for any specific case are transmitted electronically to the local investigator and coordinator on a structured table. After evaluation and resolution of any inconsistencies, the local investigators return this table to the principal investigators, who conclude the audit by retaining, modifying or excluding the case.

Another quality control procedure that has been developed consists of technical visits to the centers, when evaluation is made of the working conditions of the equipment supplied, the appropriateness of the filing system used to store the manual forms, the use of the manual of operations and the particular strategies used to locally identify cases. A random check of selected patient forms is also made and the consistency of the data previously collected by the local investigators is verified. A report is then prepared for the local and central team. If a problem/situation arising from this visit is considered to be of general interest for all centers, a note is prepared and circulated among all research staff.

As initially planned, the availability of the professionals involved was crucial in controlling the network. In addition to the local staff, the existence in the coordinating center of a principal investigator, general and deputy coordinators, research assistants, network manager, system analyst, statistician, accounts manager and other technical assistants has proved to be essential for the follow-up of surveillance on such a broad scale.

Discussion

The development of a prospective surveillance system for severe maternal morbidity in Brazil resulted in the National Network for the Surveillance of Severe Maternal Morbidity [27]. This is an innovative scientific initiative based on the experience acquired in the area by a research group on maternal morbidity and mortality at the coordinating center. In addition, this corresponds to the first time the new WHO criteria for maternal near miss will be prospectively used and validated. The full process was guaranteed by financial resources obtained from Brazilian funding agencies. These funds enabled the necessary infrastructure, including computers, the internet server, software, human resources to perform the surveillance and notification of data, the entire core organization of the study and the expenses involved in traveling to training meetings and technical visits. Nevertheless, these resources could be considered small taking into account the scale of the network structure, the complexity involved in controlling the quality of data collection and the duration of surveillance.

The decision to use an open data collection system specifically developed to support clinical studies rendered the implementation process less expensive and more practical. Although similar systems have already been used in developed countries to collect data on other subjects [16], to the best of our knowledge this is the first system developed for the prospective, widespread collection of data on severe maternal morbidity, thus permitting current epidemiological surveillance. More widespread analyses on the occurrence of severe maternal morbidity in Canada, for instance, were obtained using databases containing information routinely collected in healthcare services [25].

Meetings were of crucial importance for the development of a homogenous study. Situations differ greatly from one center to another as a result of their diverse geographical locations and resources available, although all of them were tertiary health facilities with neonatal intensive care units. Regarding their institutional capacity of providing appropriate care to obstetric complications, some of them are also provided with obstetrical ICU, some with general ICU and few have no ICU at

all. The training allowed to update electronic and support material, a fruitful debate and the investigators to share their individual experiences. Communication between the centers, including discussions on problems and suggestions, was conducted by e-mail, ensuring a quick and cheap solution.

Data collection was initiated before the system could be tested by the investigators themselves in their own work environment. This resulted in the need to modify the form and the manual of operations after the first month of data collection. This may be considered a limitation in the planning and implementation of this study, highlighting the importance of pilot studies once the system is already fully operational in order to solve any difficulties or inconsistencies detected early. Despite that, all the updates required could be considered minor, involving completion of the electronic form and the definition of a few variables. Following these adjustments, no other changes have been required.

The manual of operations incorporated around 90% of the queries raised by the investigators prior to review and this efficacy increased following the modifications. The entire data entry procedure is described in detail there, including illustrations taken from the system itself for guidance. Nevertheless, many of the investigators sought advice before consulting the manual. This shows that reading instructions prior to initiating surveillance is a mandatory step to ensure that the process flows as effectively as possible.

Another possible limitation of the study would be that this kind of surveillance would identify only cases delivering in hospitals or health care facilities. However, nowadays, fortunately this is no longer a limitation in Brazil, considering the vast majority of deliveries occur in hospitals. Anyway, the new WHO criteria for identifying maternal near miss cases has a set of criteria that could theoretically be applied to any setting, even for community deliveries.

Currently the network has already finished its data collection's activities, with more than nine thousand and five hundred of cases of potentially life threatening and maternal near miss condition s included in the database, a number much higher than what was initially expected. The initiation of data collection coincided with the H1N1 influenza epidemic [30], which may have led to an increase in the occurrence of severe cases. Indeed, one of the changes made to the system was to add this diagnosis to the form.

Taking into account this partial experience, a next special concern arises on how to guarantee sustainability for a routine surveillance in a national environment. Considering that the process has showed to be more efficient in places where the form for identifying any potentially life threatening conditions or maternal near miss was routinely implemented, this should probably be an important content of a package directed to a nationwide system for surveillance of severe maternal morbidity. The development of a national electronic database system could facilitate the interpretation and management in different settings, by different professionals, and allow adaptation to local reality. To be more effective and complete, probably the surveillance might be a governmental strategy with scientific support by researchers and/or universities with expertise in the field. The Ministry of Health could enhance hospitals participation through supporting such surveillance as a public health policy. It could be first piloted as an official process in some facilities that had already participated in the current initiative, before a broader national implementation. The government could also enable adaptation of health information systems in use nowadays to the maternal morbidity surveillance needs.

Finally, there is an interesting point that appeared when this network first went into operation that should be the subject of a more in-depth qualitative investigation in a near future. Although this current project consists of a cross-sectional, observational study for the surveillance and detection of the occurrence of episodes of severe maternal morbidity in the participating centers, there have been emphatic reports from the network participants at each center that implementation and participation in this system has generated interventions that were not routine at these centers, including the use of some evidence-based interventions that had not yet been adopted (such as the routine prophylactic use of uterotonics at all deliveries), the review of the criteria of severity in obstetrical cases for referral to intensive care units and earlier request for specialist services to help manage cases in which specific dysfunctions and organ failure are detected, among others.

Conclusions

The expectation generated following implementation of the National Network for Surveillance of Severe Maternal Morbidity is that it will lead to an increase in the production of knowledge on information technology and the surveillance of health events. The pioneering use of the criteria for near miss recently defined by the WHO [5] may permit validation of these criteria for later studies on a worldwide level. Hopefully other developing countries, and even developed countries, could implement similar surveillance systems and increase the consistency of data on maternal health. This increases the possibility of implementing actions that would indeed lead to a reduction in the unnecessary deaths of pregnant or postpartum women worldwide, as well as possibly also decreasing the burden of disease resulting from this condition for the many women who survive severe

maternal morbidity. Therefore this initiative could complement the global strategy to reduce maternal mortality.

Abbreviations

MDG: millennium development goal; WHO: World Health Organization

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Authors' contributions

The idea for the study arose in a group discussion among all the authors. The first version of the manuscript was drafted by SMH and JGC, and then complemented with the suggestions of the others. JGC supervised the entire process. All authors contributed to the development of the study protocol and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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7.3. Anexo 3 – Artigo referente à Rede Brasileira de Vigilância de Morbidade Materna Grave

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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7.4. Anexo 4 – Indicadores do Cuidado Obstétrico

Razão de Condições Potencialmente ameaçadoras da Vida (RCPAV) é calculada pelo número de mulheres com condições potencialmente ameaçadoras de vida, dividido por número de nascidos vivos por 1000.
Razão de Morte Materna (RMM) é calculada pelo número de mortes maternas dividido pelo número de nascidos vivos por100. 000.
Razão de *Near Miss* Materno (RNMM) é calculada pelo número de mulheres com *Near Miss* Materno dividido pelo número de nascidos vivos por 1000.
Razão de Desfecho Materno Grave (RDMG) é calculada pelo número de mulheres que evoluíram para a morte somado ao número de mulheres com *Near Miss*, dividido pelo número de nascidos vivos por 1000.
Razão de *Near Miss* Materno: Razão de Morte Materna (RNMM: RMM): refere-se à proporção entre RNMM e RMM, também conhecida pelo número de casos por fatalidade.
Índice de Mortalidade (IM) é calculado pelo número de mortes maternas dividido pelo número de mortes maternas somado ao número de mulheres com *Near Miss*.

7.5. Anexo 5 – Rede Brasileira de Estudos em Saúde Reprodutiva e Perinatal

CENTROS PARTICIPANTES

Maternidade Cidade Nova Dona Nazarina Daou	Manaus, AM
Maternidde Climério de Oliveira	Salvador, BA
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Hospital Geral Dr. César Cals	Fortaleza, CE
hospital Geral de Fortaleza	Fortaleza, CE
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7.6. Anexo 6 – Formulário de Coleta Manual

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
[ ] 2 obesidade
[ ] 3 baixo peso
[ ] 4 diabetes mellitus
[ ] 5 tabagismo
[ ] 6 doenças cardíacas
[ ] 7 doenças respiratórias
[ ] 8 doenças renais
[ ] 9 anemia falciforme-talassemia
[ ] 10 HIV/AIDS
[ ] 11 tireoidopatias
[ ] 12 doenças neurológicas / epilepsia
[ ] 13 colagenoses
[ ] 14 neoplasias
[ ] 15 outro
[ ] 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 tireotóxica [ ] 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
[ ] 2 acesso venoso central
[ ] 3 admissão em UTI
[ ] 4 hospitalização prolongada (>7 dias)
[ ] 5 intubação não relacionada à anestesia
[ ] 6 retorno à sala cirúrgica
[ ] 7 histerectomia/laparotomia
[ ] 8 uso de sulfato de magnésio
[ ] 9 outro proc. cirúrgico maior
[ ] 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
[ ] 2 gasping
[ ] 3 FR > 40 ou < 6
[ ] 4 choque
[ ] 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
[ ] 9 acidente vascular cerebral
[ ] 10 convulsão não controlada – paralisia total
[ ] 11 icterícia na presença de pré-eclâmpsia
[ ] 88 não houve / não consta

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

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: [ ]