EDILBERTO ALVES PEREIRA DA ROCHA FILHO

Hemorragia como causa de complicação obstétrica na Rede Brasileira de Vigilância de Morbidade Materna Grave

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP, para obtenção do Título de Doutor em Ciências da Saúde, área de concentração em Saúde Materna e Perinatal.

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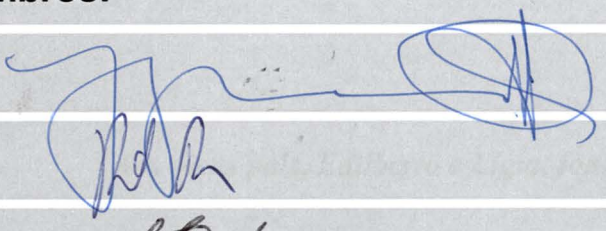
1. 
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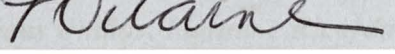
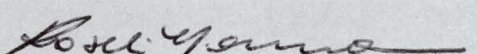
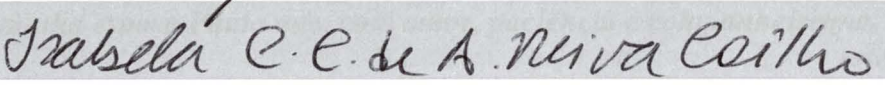
3. 
4. 
5. 

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Dedico este trabalho...

Aos meus pais, Edilberto e Lígia, fontes primárias de amor e sabedoria.

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O meu muito obrigado!

Sumário

Símbolos, Siglas e Abreviaturas

AIH – *Antepartum and intrapartum hemorrhage*

CPAV – Condição potencialmente ameaçadora da vida

DPP – Descolamento prematuro de placenta

EP – *Ectopic pregnancy*

GE – Gestação ectópica

HAI – Hemorragia ante e intraparto

HPP – Hemorragia pós-parto

ICU – *Intensive care unit*

LB – *Live births*

MD – *Maternal death*

MM – Morte materna

MMG – Morbidade materna grave

MNM – *Maternal near miss*

MNMR – *Maternal near miss ratio*

NMM – Near miss materno

NV – Nascidos vivos

OMS – Organização Mundial da Saúde

PA – Placental abruptio

PLTC – Potentially life threatening condition

PP – *Placenta previa*

PPH – *Postpartum hemorrhage*

PR – *Prevalence ratio*

SHO – Síndromes hemorrágicas obstétricas

SMM – *Severe maternal morbidity*

SMO – *Severe maternal outcome*

SMOR – *Severe maternal outcome ratio*

UTI – Unidade de terapia intensiva

WHO – World Health Organization

Resumo

Objetivo: Avaliar a ocorrência de complicações graves e óbitos associadas a gravidez ectópica (GE) e a hemorragias ante e intraparto (HAI) e pós-parto (HPP) entre mulheres da Rede Brasileira de Vigilância de Morbidade Materna Grave.

Métodos: Estudo de corte transversal multicêntrico realizado em 27 unidades de referência obstétrica no Brasil entre julho de 2009 e junho de 2010. Foi avaliada a ocorrência de condições potencialmente ameaçadoras da vida (CPAV), *near miss* materno (NMM) e mortes maternas (MM) associadas com GE, HAI e HPP em 9.555 mulheres identificadas como tendo alguma complicação obstétrica. Características sóciodemográficas e obstétricas e o uso de critérios de manejo nestas hemorragias graves também foram avaliados. Foram calculadas as razões de prevalência (RP) com seus respectivos intervalos de confiança de 95% ajustados para o efeito de cluster e análise de regressão logística múltipla para identificar os fatores associados de forma independente com a ocorrência de resultado materno grave (*Severe Maternal Outcome* - SMO=NMM+MM).

Resultados: Das 9.555 mulheres com complicações obstétricas, 312 (3,3%) tiveram complicações por GE, sendo 286 (91,7%) CPAV, 25 (8,0%) NMM e 1 (0,3%) MM. HPP foi a causa principal entre 1192 mulheres (12,5%), sendo 981 CPAV, 181 NMM e 30 MM. HAI ocorreu em 8% (767) das mulheres que experimentam algum tipo de complicação obstétrica e foi responsável por 7,1% (613) dos casos de CPAV, 18,2 % (140) de NMM e 10% (14) das MM. Mulheres com GE complicada tiveram maior risco de transfusão sanguínea, laparotomia e menor risco de admissão em UTI e tempo prolongado de internação do que mulheres com outras complicações. Houve cuidado deficiente ou

demoras no atendimento associado a casos de GE complicados. Os fatores associados ao melhor resultado foram uma cicatriz uterina prévia e ser não branca. Entre as mulheres que apresentaram HPP, a idade materna, idade gestacional precoce, cicatriz uterina anterior e cesariana prévia foram os principais fatores associados com maior risco de ocorrência de SMO. Essas mulheres também tiveram uma maior proporção de transfusão sanguínea e retorno para a sala operatória. Já para as que apresentaram HAI, a idade materna e cesariana anterior foram independentemente associadas a este maior risco.

Conclusão: O aumento da morbidade materna devido a GE aumentou a conscientização sobre a doença e seu impacto sobre a vida reprodutiva feminina. A hemorragia pós-parto persiste como uma das principais complicações obstétricas e importante causa de morbidade e morte materna no Brasil. O conhecimento dos fatores associados a um maior risco de ocorrência de SMO pode ser útil para melhorar a qualidade da atenção obstétrica e dos resultados maternos. SMO devido a hemorragia ante e intraparto foi altamente prevalente entre as mulheres brasileiras. Alguns fatores de risco, em particular a idade materna e cesareana prévia, foram associados com a ocorrência desta complicação hemorrágica. Os serviços obstétricos devem desenvolver diretrizes e intervenções específicas para prevenir a morbidade materna grave para cada condição hemorrágica obstétrica específica identificada.

Palavras chaves: Morbidade materna; Mortalidade materna; *Near Miss* materno; Hemorragia pós-parto; Gravidez Ectópica.

Summary

Objective: To evaluate the occurrence of severe obstetric complications associated with ectopic pregnancy (EP) and antepartum or intrapartum (AIH) and postpartum hemorrhage (PPH) among women in the Brazilian Network for the Surveillance of Severe Maternal Morbidity.

Methods: A multicenter cross-sectional study conducted in 27 referral obstetric units in Brazil between July 2009 and June 2010. The occurrence of potentially life-threatening conditions (PLTC), maternal near miss (MNM) and maternal death (MD) associated with EP, AIH and HPP were evaluated among 9,555 women identified as having some obstetric complication. Socio demographic and obstetric characteristics and use of management criteria in these severe hemorrhages were also assessed. Prevalence ratios (PR) were calculated with their respective 95% confidence intervals adjusted for the cluster effect and multiple logistic regression analysis to identify factors independently associated with the occurrence of severe maternal outcome (SMO = MNM + MD) .

Results: Among the 9,555 women with obstetric complications, 312 (3.3%) had complications due to EP, with 286 (91.7 %) PTLC, 25 (8.0%) MNM and 1 (0.3 %) MD. HPP was the leading cause in 1192 women (12.5 %), with 981 PTLC, 181 MNM and 30 MD. AIH occurred in 8% (767) of women experiencing any type of obstetric complication and accounted for 613 (7.1%) of the PTLC cases, 140 (18.2%) of MNM and 10% (14) of MD. Women with complicated PE had a higher risk of blood transfusion, laparotomy and lower risk of ICU admission and prolonged hospitalization than women with other complications. There was a substandard care or delays associated with cases of complicated EP. The factors associated with a better outcome were a previous uterine scar and to be non-white. Among women who had PPH, maternal age, early

gestational age, previous uterine scar and previous cesarean delivery were the main factors associated with a risk of SMO. These women also had a higher proportion of blood transfusion and return to operating room. For those who had AIH, maternal age and previous cesarean section were independently associated with this increased risk.

Conclusion: Increased maternal morbidity due to EP raised awareness about the condition and its impact on female reproductive life. Postpartum hemorrhage persists as one of the main obstetric complication and important cause of maternal morbidity and mortality in Brazil. The knowledge of factors associated with a severe maternal outcome (SMO=MNM+MD) could be useful for improving the quality of obstetric care and maternal outcomes. SMO due to antepartum and intrapartum hemorrhage was highly prevalent among Brazilian women. Some risk factors, maternal age and prior cesarean delivery in particular, were associated with the occurrence of this hemorrhagic complication. Care providers should develop specific guidelines and interventions to prevent severe maternal morbidity for each specific obstetric hemorrhagic condition identified.

Keywords: Maternal morbidity; Maternal mortality; Maternal near miss; Postpartum hemorrhage; Ectopic pregnancy.

1. Introdução

A mortalidade materna é um tópico muito relevante em saúde pública. É grave a situação de muitas populações em várias partes do mundo, notadamente sudeste asiático e África subsaariana, que convivem há muito tempo com taxas bastante altas e contribuem para uma alta razão de mortalidade materna global. O número de óbitos maternos por 100 mil nascidos vivos é da ordem de 210 em todo o mundo, com 289.000 mortes maternas ao ano, das quais 85% em países dessas regiões. Apesar de decrescente nos países de baixa e média renda, quando analisados de forma global, a razão de mortalidade materna ainda persiste em níveis bastante elevados. Estes países são responsáveis por 99% das mortes no mundo (286.000 óbitos) (WHO, 2013).

A Organização Mundial de Saúde (OMS) tentou reduzir esse problema através de várias iniciativas, como o *Safe Motherhood* (Maternidade Segura), e incluiu o problema nos chamados "objetivos de desenvolvimento do milênio" (*Milennium Development Goals*), com a intenção de reduzir em três quartos da razão de mortalidade materna até 2015 (WHO, 2013). Aos poucos, percebeu-se que essa redução talvez possa ser feita lançando-se mão de meios mais sutis de abordagem, como por exemplo, estudar, entender e prevenir a morbidade materna grave.

A morbidade materna grave (MMG) é definida como uma condição potencialmente ameaçadora à vida, subdividida em *near miss*, descrita como situações de "quase-perda", em que a paciente efetivamente correu um risco apreciável de óbito, mas sobreviveu e em MMG não *near miss*, todas as outras

condições potencialmente ameaçadoras à vida que não tinham um risco tão grande (Say et al., 2009).

A prevalência mundial de morbidade materna grave varia de 0,8 a 8,3%, baseado em relatos de várias partes do mundo, reunidos em metanálise da Organização Mundial da Saúde (Say et al., 2004). Como é mais frequente do que o óbito, facilita o estudo de suas causas, especialmente porque ambas as condições compartilham várias características clínicas comuns.

O esforço para abordar adequadamente o problema da mortalidade materna pode ser melhor aproveitado no combate à morbidade materna grave, na busca e identificação de lacunas no conhecimento e na adequação dos resultados de pesquisas com boa metodologia para a prática médica (Cecatti et al., 2007). A idéia subjacente é facilitar a adoção de medidas preventivas, factíveis de implementação em todos os níveis de atenção à saúde que atuem mais precocemente na cadeia de eventos que leva da morbidade materna grave à morte.

As síndromes hemorrágicas obstétricas (SHO) se subdividem em anteparto, intraparto e pós-parto. Entre as causas de hemorragias anteparto, que representam 5-6% de todas as gestações, sobressaem-se a placenta prévia e o descolamento prematuro de placenta normalmente inserida. Entre as causas de hemorragia intraparto, são mais frequentes as lacerações de trajeto e a rotura uterina (Mercier et al., 2008). Entre as causas de hemorragia pós-parto, destacam-se a atonia uterina – mais de 80% de todas as causas pós-parto - inversão uterina aguda, laceração de trajeto, retenção placentária e distúrbios de coagulação (Amy, 1998; Akhter, 2003; Lewis, 2007).

Atualmente, as síndromes hemorrágicas representam, mundialmente (embora não nos países desenvolvidos e nos em via de desenvolvimento, como o Brasil), a maior causa de mortalidade materna, seja por falta de assistência médica adequada ou pela ausência de suporte básico de vida, a despeito da existência de protocolos bem definidos de prevenção, especialmente enfatizando o uso rotineiro de 10UI de ocitocina no terceiro período do parto (WHO, 2012).

A hemorragia pós-parto é uma das principais causas de mortalidade e morbidade materna grave (Amy, 1998; Wildman & Bouvier-Colle, 2004, Lewis, 2007). É a principal causa de mortalidade materna, tanto em países de baixa como média renda (Akhter et al., 2003; Geller et al., 2004). A hemorragia pós-parto é relatada com uma freqüência entre 2 a 4% dos partos vaginais e de 6% após cesarianas. A atonia uterina é a principal dentre todas as SHO, ocorrendo em cerca de 50% destas (Amy, 1998; Lewis, 2007). A SHO é uma entidade que pode levar à morte rapidamente, em menos de 2 horas. O uso de ocitócitos e de outras técnicas de manejo podem salvar muitas vidas. Uma importante arma utilizada no tratamento da hemorragia pós-parto é a transfusão sanguínea, que reduz a morbidade e acelera a recuperação da qualidade de vida (Wildman et al., 2004; Jansen et al., 2005).

Algumas medidas ou técnicas para o manejo das SHO, que não são usualmente praticadas em países de alta renda ainda tem um lugar de importância em países em de baixa e média renda, apesar de não mais recomendadas pela OMS, como por exemplo, o uso de *packing* uterovaginal ou tamponamento uterino (Bagga et al., 2004; Akhter et al., 2003).

O *near miss* é um novo termo utilizado em obstetrícia e surgiu para solucionar uma questão que dificulta os estudos sobre óbito materno. A mortalidade materna (MM) é o principal indicador utilizado para monitorar a saúde materna. Apesar desta ainda ser muito elevada, os estudos que utilizam a morte materna como variável de desfecho geralmente enfrentam dificuldades devido ao baixo número absoluto dos casos. No entanto, para cada mulher que morre, muitas outras sofrem complicações na gravidez, sejam elas hipertensivas, hemorrágicas, infecciosas ou de outra natureza. Algumas destas são condições menos graves e podem ser caracterizadas como Condições Potencialmente Ameaçadoras da Vida (CPAV). No entanto, outras são bastante graves e com chances reais de levar ao óbito. Assim, com o passar do tempo, observou-se o surgimento, principalmente em Unidades de Terapia Intensiva (UTIs), de uma grande quantidade de pacientes que não tinham como desfecho o óbito, mas que compartilhavam com estas muitas de suas graves

características (Say et al., 2004; Say et al., 2009). São pacientes que tiveram morbidade do tipo *Near Miss* (NMM). O *near miss* materno é definido pela OMS como uma mulher que quase morreu, mas sobreviveu a complicações durante a gestação, parto ou até 42 dias após o seu término (Pattinson et al., 2009). Para ser considerada um caso de n*ear Miss,* a paciente deverá apresar ao menos um critério de gravidade (clínico, laboratorial ou de manejo – ANEXO 1). Caracterizar a morbidade do tipo *near miss* é valioso para monitorar a qualidade da base hospitalar obstétrica e para avaliar a incidência de complicações potencialmente fatais. Casos de morbidade near miss também podem fornecer um grupo de comparação apropriado, tanto para revisão dos casos clínicos como para a análise epidemiológica (Geller et al., 2004). Utilizar o *near miss* como modelo para o estudo do óbito materno traz ainda uma série de vantagens: permite identificar sinais precoces de condições ameaçadoras da vida materna, fatores de risco, tem uma melhor aceitação que as mortes maternas e ainda permite uma maior facilidade na análise dos dados, já que possui uma frequência maior que a do óbito (Cecatti et al., 2007; Say et al., 2009; Haddad et al., 2011).

A SHO se configura como uma das principais causas de mortalidade materna e também como causa significativa de *near miss.* Uma análise retrospectiva de quatro anos consecutivos (de 2000 a 2003) realizada na Índia usando o sistema de escores descrito por Geller para medir os fatores de risco de mortalidade e de *near miss* nas SHO primárias mostrou que a frequência de mortes foi menor que a deste tipo de morbidade grave - 6,18% contra 10,67% (Geller et al., 2004) e que a demora na transferência de casos de SHO para centros mais preparados e a falta de uma conduta mais ativa no terceiro período do parto foram responsáveis pela maioria dos eventos adversos (Kaul et al., 2006). Estudos de análises de óbitos maternos mostraram que muitas mortes se dão por manejo inadequado e assistência deficitária no diagnóstico e no tratamento da hemorragia (Zhang et al., 2005; CNEMM, 2006). Achados na literatura sugerem que a implementação de diretrizes clínicas rigorosas

propiciam uma melhora nos indicadores de hemorragia pós-parto (Deneux-Tharaux et al., 2008; Winter et al., 2007).

Esse estudo propõe-se a avaliar a ocorrência de complicações maternas (condições potencialmente ameaçadoras da vida materna, *near miss* materno e óbitos maternos) atribuíveis às Síndromes Hemorrágicas Obstétricas em um grupo de gestantes e puérperas incluídas na Rede Nacional de Vigilância de Morbidade Materna Grave implementada no Brasil (Cecatti et al., 2009). Objetiva ainda identificar as características sócio-demográficas e obstétricas das mulheres associadas à pior evolução para óbito ou near miss e a frequência de critérios de manejo de *near miss* entre estas.

2. Objetivos

2.1. Objetivo Geral

Avaliar a ocorrência de complicações obstétricas graves associadas a hemorragias entre as mulheres da Rede Brasileira de Vigilância de Morbidade Materna Grave.

2.2. Objetivos Específicos

1. Avaliar a ocorrência de complicações maternas graves associadas à gravidez ectópica.
2. Avaliar a ocorrência de complicações maternas graves devido à hemorragia pós-parto e seus fatores associados.
3. Avaliar a ocorrência de complicações maternas graves associadas a hemorragias ante e intraparto.

3. Sujeitos e Método

Desenho do estudo

Análise secundária de um banco de dados obtido de um estudo de corte transversal multicêntrico, realizado durante um período de doze meses, de julho de 2009 a junho de 2010, em 27 unidades obstétricas de referência nas diversas regiões geográficas do Brasil. Os dados foram colhidos da Rede Brasileira de Vigilância de morbidade materna grave (Cecatti et al., 2011; Haddad et al., 2011) em um estudo de corte transversal, através de uma vigilância prospectiva dos prontuários das pacientes no momento de sua alta hospitalar.

Instrumento para coleta de dados

Em cada centro, um coordenador local da pesquisa colheu os dados utilizando formulários manuais e então os inseriu *on-line* em uma plataforma eletrônica (OpenClinica® versão 3.0 - Akaza Research, Waltham, MA, USA). Posteriormente, estes foram verificados e validados por um investigador local. Foi realizado controle da qualidade dos dados em cada centro participante. Pessoal treinado pelo centro de coordenação realizou visitas de acompanhamento e analisou casos selecionados aleatoriamente (cerca de 5% dos casos de cada centro). Informações mais detalhadas sobre os aspectos metodológicos do estudo podem ser encontradas em outras publicações (Cecatti et al., 2011; Haddad et al., 2011).

Os dados foram obtidos através da extração dos mesmos da base de dados da pesquisa original, contidos no programa OpenClinica®, inicialmente exportados como planilha do software Excel®. Está estruturado em um questionário de 80 itens (Anexo 1), dos quais uma parte foi utilizada para o presente trabalho:

Dados pessoais – questões 1 a 11;
Dados obstétricos – questões 15 a 28;
Condições maternas pré-existentes – questões 42 a 44;
Condições potencialmente ameaçadoras – 45 a 48;
Critérios de near miss – questões 56 a 62;
Desfecho materno – questões 63 a 64.

Tamanho Amostral

O tamanho amostral foi estimado em 75.000 partos. Cobrindo um total de 82.144 nascimentos vivos, verificou-se a presença de alguma condição potencialmente ameaçadora da vida (CPAV), de near miss materno (NM) e de óbitos materno (MM), de acordo com a nova definição e critérios da OMS (Say et al., 2009). Em todos os casos incluídos foram analisadas as características sócio-demográficas, clínicas, obstétricas, de pré-natal, de complicações no parto e/ou puerpério, dados sobre demoras no atendimento e condições do recém-nascido.

Calculou-se a prevalência dos diferentes tipos de complicações hemorrágicas entre as mulheres que apresentaram CPAV, NM e MM. Foi ainda avaliada a presença de critérios de manejo de gravidade entre as mulheres com alguma hemorragia ante ou intraparto e as mulheres que apresentaram alguma outra complicação, estimando-se a razão de prevalência (RP) e seus respectivos intervalos de confiança (IC 95%). Da mesma forma, analisou-se as características sóciodemográficas e obstétricas das mulheres com complicações hemorrágicas ante ou intraparto, estimando-se o risco de um resultado materno grave (*near miss* ou óbito). Verificou-se a presença dos

critérios para *near miss* da OMS entre as mulheres com complicações hemorrágicas ante ou intraparto**.** Finalmente, realizou-se uma análise múltipla por regressão logística para identificar os fatores independentemente associados com a maior gravidade das complicações por hemorragia ante ou intraparto.

Variáveis

São apresentadas as definições das variáveis analisadas, registradas no banco de dados, de acordo com dados obtidos dos prontuários médicos.

Variável independente

Síndrome Hemorrágica: Definida como sangramento obstétrico caracterizado clinicamente como derivado de gestação ectópica, hemorragia ante e intra-parto ou hemorragia pós-parto.

Variável dependente

N*ear miss* materno: presença de um ou mais critérios clínicos e/ou laboratoriais e/ou de manejo descritos abaixo:

- Critérios clínicos diagnósticos: *gasping*, frequência respiratória maior que 40ipm ou menor que 6ipm, choque, oligúria não responsiva a fluídos ou diuréticos, distúrbio de coagulação, perda de consciência durante 12 horas ou mais, ausência de consciência e ausência de pulso ou batimento cardíaco, acidente vascular cerebral, convulsão não controlada e/ ou paralisia total, avaliados de acordo com os dados de prontuários médicos registrados no banco de dados.

- Critérios laboratoriais: saturação de oxigênio menor que 90% por mais de 60 minutos, relação PaO2/FiO2 menor que 200, creatinina maior que 300mmol/dl ou maior igual a 3,5mg/dl, bilirrubina maior que 100mmol/dl ou maior igual a 6,0mg/dl, pH menor que 7,1, lactato maior que 5, trombocitopenia aguda menor que 50.000 plaquetas, ausência de consciência associada à presença de glicose e cetoacidose na urina,
- Critérios de manejo: necessidade de uso de droga vasoativa contínua, histerectomia puerperal por hemorragia ou infecção, transfusão de 5 ou mais concentrados de hemácias, intubação e ventilação por tempo maior que 60 minutos não relacionada a anestesia, diálise para insuficiência renal aguda, ressuscitação cardiopulmonar

Variáveis de controle

- Idade da mulher em anos completos, calculada pela data do nascimento.
- Cor da pele: conjunto de características socioculturais e fenotípicas, identificadas pela observação ou declaração da própria mulher. Categorizada em:

    -Brancas: mulheres com a pele branca ou parda de origem européia ou latino-americana

    -Não-brancas: mulheres que tenham a pele preta, mulheres pardas de origem africana, ou de origem oriental, e aquelas com características originárias da população autóctone do país.

- Escolaridade: categorizada em: analfabeta, ensino fundamental completo ou incompleto, ensino médio completo ou incompleto ou ensino superior.
- Peso em quilogramas
- Altura em metros.
- Pré-natal prévio no serviço: categorizada em sim (acompanhamento pré-natal no serviço em que foi internada independente do número de consultas) ou não (se nunca tiver sido atendida no serviço nem passado em consulta de triagem para agendamento de consulta)
- Número de gestações anteriores: número total de gestações da mulher, incluindo gestações que terminaram em aborto, prenhez ectópica ou gestação molar. Nesta variável deve-se incluir a gestação atual.
- Número de partos anteriores: número de partos ocorridos após 22 semanas, incluindo partos vaginais, cesáreas e partos vaginais assistidos, excluindo-se a gestação atual.
- Número de abortos anteriores: número de gestações finalizadas antes de 22 semanas ou com expulsão de produto de concepção com menos de 500g, excluindo-se a gestação atual.
- Número de cesáreas anteriores: número total de cesáreas anteriores, excluindo-se a gestação atual.
- Número de filhos vivos: número total de filhos vivos.
- Anos desde o último parto: anos completos entre o último parto e a gestação atual, informado pela paciente.

- Presença de cirurgia uterina prévia: qualquer procedimento que tenha resultado em cicatriz uterina diferente de histerotomia segmentar transversa, essa variável será categorizada em sim ou não.
- Número de consultas no pré-natal: número total de consultas de pré-natal, obtidas por observação do cartão de pré-natal ou informação da paciente.
- Idade gestacional na internação: calculada pela data da última menstruação ou primeiro exame de ultrassom. A idade gestacional deve ser completa. Quando a admissão for pós-parto ou a idade gestacional for ignorada, isso deve ser informado.
- Forma de início do trabalho de parto: essa variável será categorizada em:

- Espontâneo: quando ocorrer início natural das contrações uterinas, dilatação e esvaecimento cervical, independente da condução do mesmo posteriormente com métodos farmacológicos como ocitocina ou misoprostol.

- Induzido: quando o trabalho de parto se iniciar devido uso de métodos farmacológicos ou mecânicos (misoprostol, ocitocina, balão cervical, laminária).

- Sem trabalho de parto: quando a resolução da gestação ocorrer antes do início do trabalho de parto.

- Aborto: para os casos de prenhez ectópica ou aborto.

- Continua grávida: quando a paciente receber alta hospitalar ainda gestante.

- Idade gestacional da resolução da gestação: calculada pela data da última menstruação ou primeiro exame de ultrassom. A idade gestacional deve ser

completa. Quando a paciente receber alta hospitalar ainda gestante deve-se informar que ela continua grávida.

- Forma de resolução da gestação: categorizada em:

  - Parto vaginal: parto via vaginal sem uso de instrumental auxiliar.

  - Vaginal operatório: parto vaginal com utilização de qualquer instrumental ou procedimento complementar para ultimar o parto (fórceps, vácuo-extrator ou versão cefálica).

  - Aborto: expulsão de produto de concepção antes de 22 semanas de gestação ou com peso abaixo de 500g.

  - Prenhez ectópica: gestações em que o óvulo fecundado estiver implantado fora da cavidade endometrial, podendo sua resolução ser cirúrgica ou clínico farmacológica.

  - Parto cesárea antes do início do trabalho de parto.

  - Parto cesárea após início do trabalho de parto.

  - Continua grávida: paciente que receber alta hospitalar ou evoluir para óbito sem a ocorrência do parto.

- Condições mórbidas ou riscos prévios à gestação. Categorizada em: hipertensão arterial crônica, obesidade, cardiopatia, baixo peso, diabetes mellitus, tabagismo, doença respiratória, doença renal, anemia falciforme-talassemia, HIV-AIDS, tireoidopatias, doença neurológica/epilepsia, colagenoses, neoplasias, drogadição.
- Desfecho materno. Resultado do internamento, categorizada em alta médica, alta a pedido, transferência , evasão e óbito

Processamento e análise dos dados

Os resultados foram analisados utilizando-se os softwares SPSS® (*Statistical Package for the Social Sciences*) e EpiInfo®3.5.3 através da planilha Excel® gerada pelo software de coleta OpenClinica®.

Foi utilizada estatística descritiva padrão para obter as características demográficas da população do estudo. A associação das síndromes hemorrágicas com morbidade materna grave foi avaliada através de testes paramétricos de qui-quadrado ou teste exato de Fisher. Foram ainda estimadas as razões de prevalência com intervalo de confiança de 95%, considerando-se como estatisticamente significativos valores de $p<0,05$. Também foi estimado o papel de cada fator causal da hemorragia, inicialmente em análise com qui-quadrado ou teste exato de Fisher. Uma análise multivariada por regressão logística foi também realizada para identificar os fatores independentemente associados com a ocorrência de morbidade e cada tipo de hemorragia considerada. Para a análise multivariada, utilizou-se a regressão de Poisson múltipla.

Aspectos éticos

O estudo foi aprovado pelo Comitê de Ética em Pesquisa (CEP) do centro coordenador do estudo (parecer do CEP: 097/2009 / CAAE: 0071.1.146.000-09). Posteriormente, foi aprovado também nos respectivos CEPs de cada centro participante e pelo Conselho Nacional de Ética em pesquisa (CONEP). (ANEXO 2).

As mulheres inseridas no estudo foram identificadas por números, de forma que a sua identificação não era possível por nenhum dos centros, mantendo-se a confidencialidade dos dados.

4. Publicações

Artigo 1:

Edilberto A Rocha Filho, Danielly S Santana, Jose G Cecatti, Maria L Costa, Samira M Haddad, Mary A Parpinelli, Maria H Sousa, Rodrigo S Camargo, Rodolfo C Pacagnella, Fernanda G Surita, Joao L Pinto e Silva. Awareness about a life-threatening condition: ectopic pregnancy in a Network for Surveillance of Severe Maternal Morbidity in Brazil. **BioMed Res Int** 2014; 965724.

Artigo 2:

Edilberto A Rocha Filho, Maria L Costa, Jose G Cecatti, Mary A Parpinelli, Samira M Haddad, Rodolfo C Pacagnella, Maria H Sousa, Elias F Melo Jr, Fernanda G Surita, Joao P Souza, for the Brazilian Network for Surveillance of Severe Maternal Morbidity Study Group. Severe maternal morbidity and near miss due to postpartum hemorrhage: results from a national multicenter surveillance study. **Int J Gynecol Obstet** 2014. Submitted.

Artigo 3:

Edilberto A. Rocha Filho, Maria L. Costa, Jose G. Cecatti, Mary A. Parpinelli, Samira M. Haddad, Maria H. Sousa, Elias F. Melo Jr, Fernanda G. Surita, Joao P. Souza & The Brazilian Network For Surveillance Of Severe Maternal Morbidity Study Group. Contribution of antepartum and intrapartum hemorrhage to the burden of maternal near miss and death in a national surveillance study. **Acta Obstet Gynecol Scand** 2014. Submitted.

4.1. Artigo 1

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Research Article

Awareness about a Life-Threatening Condition: Ectopic Pregnancy in a Network for Surveillance of Severe Maternal Morbidity in Brazil

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Objective. To assess occurrence of severe maternal complications associated with ectopic pregnancy (EP). *Method.* A multicenter cross-sectional study was conducted, with prospective surveillance of potentially life-threatening conditions (PLTC), maternal near miss (MNM), and maternal death (MD). EP complications, patient sociodemographic/obstetric characteristics, and conditions of severity management were assessed, estimating prevalence ratios with respective 95% CI. Factors independently associated with greater severity were identified using multiple regression analysis. *Results.* Of the 9.555 severe maternal morbidity patients, 312 women (3.3%) had complications after EP: 286 (91.7%) PLTC, 25 (8.0%) MNM, and 1 (0.3%) MD. Severe maternal outcome ratio (SMOR) was 0.3/1000 LB among EP cases and 10.8/1000 LB among other causes. Complicated EP patients faced a higher risk of blood transfusion, laparotomy, and lower risk of ICU admission and prolonged hospitalization than women developing complications resulting from other causes. Substandard care was the most common in more severe maternal morbidity and EP cases (22.7% MNM and MD versus 15% PLTC), although not significant. *Conclusion.* Increased maternal morbidity due to EP raised awareness about the condition and its impact on female reproductive life. No important risk factors for greater severity were identified. Care providers should develop specific guidelines and interventions to prevent severe maternal morbidity.

1. Introduction

Ectopic pregnancy (EP) is a recurrent medical condition. It is a significant cause of maternal mortality and morbidity, especially in low-income and middle-income countries, where the majority of patients present late with tubal rupture and hemodynamic compromise [1]. The incidence of EP is approximately 1-2% of pregnancies and 10–20 per 1,000 live births [2, 3]. The overall incidence is currently rising worldwide, possibly due to increasing pelvic inflammatory disease (PID), with persistent luminal damage [4–8].

Despite the recently observed decline in general and specific maternal mortality due to ectopic pregnancy, this remains the cause of around 4.9% of all maternal deaths in developed countries, with 3-4% in the United States and in England [5, 6, 9, 10]. In low- and middle-income countries, it is estimated that approximately 0.5% of maternal deaths are due to ectopic pregnancy, with 0.5% in Latin America, 0.5% in Africa, and 0.1% in Asia [9, 11, 12]. Ectopic pregnancy is the main cause of maternal mortality in the first trimester of pregnancy and is responsible for 80% of maternal deaths in

this phase, at least in settings where there are no restrictive laws for induced abortion [2, 5, 13].

Awareness about the impact of this condition on young fertile women and care providers is paramount, since early diagnosis can avoid severe intra-abdominal hemorrhage in tubal EP. The prevention of maternal morbidity in EP represents a major challenge to ensure improvement in women's health, since there are no identified risk factors that can clearly predict severe bleeding in these cases [3, 8].

As a secondary analysis from a multicenter cross-sectional study for the surveillance of severe maternal morbidity and near miss in Brazil [14], the aim of this study is to evaluate EP considering an innovative approach, using the WHO concepts [15] of potentially life-threatening condition (PLTC), maternal near miss (MNM), and maternal death (MD). Diagnostic criteria for the identification of the abovementioned conditions, as well as the specific sociodemographic and obstetric characteristics associated with a worse outcome of EP, will be explored. Management criteria will also be assessed.

2. Materials and Methods

A multicenter cross-sectional study was conducted in 27 referral obstetric units in diverse geographical regions in Brazil. During a 12-month period, from June 2009 to May 2010, prospective surveillance of potentially life-threatening maternal conditions (PLTC), maternal near miss (MNM), and maternal death (MD) was carried out, using the WHO criteria and classification [15–17]. Sample size was originally estimated by roughly 75.000 deliveries that should be under surveillance to identify near miss cases by using the new criterion established by the World Health Organization.

Thus, all medical charts of women admitted to participating hospitals to deliver or because they have any severe complication related do pregnancy were reviewed immediately after hospital discharge. Medical charts of women transferred to other healthcare services before completion of the case or those who died were also reviewed, in search of cases showing the WHO identifiers defined as those most frequently associated with organ dysfunction and severe morbidity. The search for information that was unavailable in the chart was carried out in other sources such as the hospital database, prenatal record forms, and transfer documents or was obtained from the healthcare team.

Data collection was conducted in a specific chart that also contained information about adequacy of health care and the occurrence of delays for getting appropriate treatment. After manual collection, the forms were filed to become accessible at the time of technical visits for quality control. The data was entered into electronic forms hosted on the project website, which was hosted on the institutional web page of the coordinating study center and sent to the central database, using the OpenClinica 3.0, a specific platform for management of clinical studies. Further details on the study and methodological aspects are included in other publications [14, 18]. Approval from the IRB of each institution and from the National Council for Ethics in Research was obtained before the beginning of the study.

Quality control was assured by several manners. Initially, before data collection began, a manual of operation was provided and coordinators of each center were trained. During data collection, each coordinator reviewed the forms, checked for typographical errors, and provided the search for data that was unavailable on the charts. The local investigator carried out a new review to identify possible inconsistencies. Finally, the national study coordinators reviewed the database, identified inconsistencies, and sent the correction report to the participating centers which were required to make the corrections [18].

During the study, consistent auditing with a set of validation and cross-checking rules as part of online data management assigned a systematic evaluation of possible delays and deficiencies in the quality of care and health system inadequacy, with data on interhospital transfer, refusal by a patient to accept treatment ("discharge requested by the patient" or "evasion"), or lack of equipment or medication. Altogether they are operationally defined as a substandard care with or without delays.

For the assessment of ectopic pregnancy associated with severe maternal morbidity, cases were divided into obstetric complications due to ectopic pregnancy and obstetric complications due to other causes. Therefore not all cases of ectopic pregnancy entered the study, but only those complicated with a specific life-threatening condition identified or those undergoing a laparotomy for treatment. Initially, the prevalence of PLTC, MNM, and MD was calculated and compared between these groups. Then the following health indicators related to maternal morbidity and mortality were estimated: the maternal near miss incidence ratio (MNM incidence ratio), severe maternal outcome ratio (SMOR, MNM + MD), maternal near miss to maternal death ratio (MNM : MD ratio), and mortality index and maternal mortality ratio (MMR), according to WHO recommendations [15].

The diagnostic criteria used for the identification of PLTC, MNM, and MD, as well as the conditions of severity management, were assessed in these same groups (ectopic pregnancy and other causes). The P value for diagnostic criteria and the prevalence ratio adjusted for cluster effect of the design with their respective 95% CI for the conditions of severity management were estimated. The correction for the cluster effect of the design was performed because each participating center was considered to be a cluster, and the correspondent heterogeneity of values within each variable among cluster was assessed as adequate [19]. With the purpose of evaluating the sociodemographic and obstetric factors possibly related to greater severity among women with complications secondary to ectopic pregnancy, two comparative groups were created: one with PLTC and the other with more severe conditions, represented by the sum of MNM and MD. Then, we calculated the prevalence ratio adjusted for cluster effect with the respective 95% CI. Finally, a multiple Poisson regression analysis was used to identify the factors independently associated with greater severity of complications due to ectopic pregnancy.

Table 1: Prevalence of potentially life-threatening conditions (PLTC), maternal near miss (MNM), and maternal deaths (MD) among complicated ectopic pregnancy cases and other causes of morbidity and their correspondent health indicators.

Morbidity/mortality	Cause		PR (95% CI) for ectopic pregnancy
	Ectopic pregnancy	Other causes	
PLTC	286 (91.7)	8359 (90.4)	1.16 (0.69–1.94)
MNM	25 (8.0)	745 (8.1)	0.99 (0.58–1.69)
MD	1 (0.3)	139 (1.5)	0.22 (0.05–1.01)
Total	**312**	**9243**	
Health indicators			LB: 82.144
MNMR	0.3/1000 LB	9.07/1000 LB	
SMOR	0.3/1000 LB	10.8/1000 LB	
MNM : MD ratio	25.0 : 1	5.4 : 1	
Mortality index	3.8%	15.7%	
MMR	1.2/100.000 LB	169.2/100.000 LB	

PR: prevalence ratio adjusted for cluster effect; PLTC: potentially life-threatening condition; MNM: maternal near miss; MD: maternal death; LB: live births; MNMR: maternal near miss ratio; SMOR: severe maternal outcome ratio; MMR: maternal mortality ratio.

3. Results

In a total of 9.555 women identified with severe complications associated with pregnancy, delivery, or postpartum period, 312 (3.3%) had complications secondary to ectopic pregnancy and 9.243 (96.7%) developed complications resulting from other causes. PLTC and MNM, respectively, occurred in a total of 8.359 (90.4%) and 745 (8.1%) women in the group with other causes and in 286 (91.7%) and 25 (8.0%) women in the EP group. MD occurred in a total of 139 (1.5%) women for the morbidity group due to other causes. There was only one death (0.3%) attributed to ectopic pregnancy (Table 1) (Figure 1). This only one case of maternal death due to ectopic pregnancy was admitted to one of the participating centers already in an extreme severe, hemorrhagic shock, and almost dying condition after a laparotomy performed in another hospital. The women died soon after admission in the intensive care unit.

The maternal near miss incidence ratio was 0.3/1000 LB among ectopic pregnancy cases and 9.07/1000 LB among the remaining causes; the severe maternal outcome ratio (SMOR) was 0.3/1000 LB among ectopic pregnancy cases and 10.8/1000 LB among the remaining causes. The MNM : MD ratio was 25 : 1 for ectopic pregnancy cases and 5.4 : 1 for the remaining causes. The mortality index was 3.8% for ectopic pregnancy cases and 15.7% for the remaining causes and the maternal mortality ratio (MMR) was 1.2/100.000 LB among ectopic pregnancy cases and 169.2/100.000 LB among other causes (Table 1).

Bleeding was the most widely used diagnostic criteria for PLTC in the identification of complicated cases of ectopic pregnancy, while, among the remaining causes, hypertension and clinical-surgical criteria were more frequently used. Infection was not identified as statistically significant for morbidity due to EP, in comparison to the remaining causes (Table 2).

Among the more severe cases, maternal near miss and maternal death (MNM and MD), the most widely used criteria for complicated EP were clinical (16 MNM cases) and management (15 MNM cases), when applying the WHO criteria for identifying near miss events. In the only MD case, clinical, laboratory, and management criteria were observed (Table 2).

When assessing the conditions of severity management, it was observed that patients who had complicated ectopic

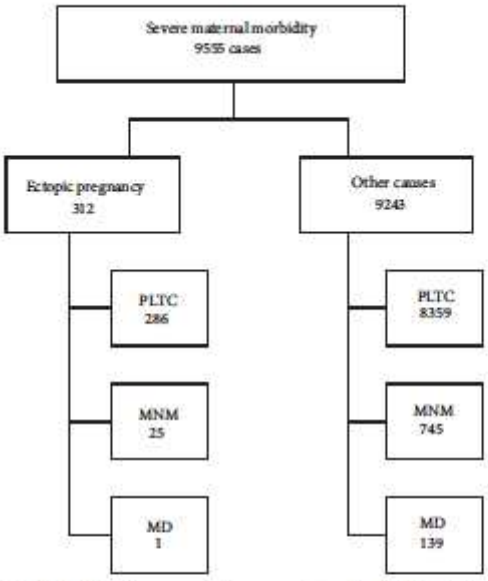

Figure 1: Flow of women with severe maternal morbidity due to ectopic pregnancy or other causes according to the final outcome in PLTC (potentially life-threatening condition), MNM (maternal near miss), or MD (maternal death).

Table 2: Prevalence of main causes of morbidity among cases complicated with ectopic pregnancy or other conditions and number of cases identified by specific WHO criteria for maternal near miss.

Causes of morbidity	Ectopic pregnancy	Other conditions	P
Hypertension	1.3	72.5	**<0.001**
Hemorrhage	94.6	21.5	**<0.001**
Infection	0.3	1.1	0.195
Clinical-surgical	4.5	10.9	**0.011**
Total	**(312)**	**(9,243)**	
WHO criteria for MNM and MD among ectopic pregnancy cases		MNM	MD
Clinical		(16)	(1)
Laboratory		(3)	(1)
Management		(15)	(1)
Total		25	1

MNM: maternal near miss; MD: maternal death. Values in bold type indicate statistically significant values.

Table 3: Estimated risk of ectopic pregnancy among maternal morbidity cases, according to conditions of severity management used.

Conditions of severity management	Ectopic pregnancy	Other conditions	PR for ectopic pregnancy	95% CI
Blood transfusion	37.2	15.7	**2.37**	**1.73–3.24**
Central venous access	2.6	3.8	0.67	0.33–1.35
ICU admission	7.7	22.6	**0.34**	**0.18–0.63**
Prolonged hospital stay (>7 days)	3.5	30.9	**0.11**	**0.05–0.25**
Nonanesthetic intubation	1.6	3.1	0.51	0.19–1.39
Return to operating room	1.6	3.4	0.48	0.14–1.64
Laparotomy	97.1	3.1	**31.39**	**21.87–45.04**
Use of magnesium sulphate	0.0	50.0	**<0.01**	**<0.01–<0.01**
Other major surgical procedures	1.0	0.8	1.27	0.30–5.31
Total	**(312)**	**(9,243)**		

PR: prevalence ratio adjusted for cluster effect; 95% CI: 95% confidence interval for prevalence ratio; ICU: intensive care unit. Values in bold type indicate statistically significant values.

pregnancy showed a higher estimated risk of blood product transfusion and laparotomy and a lower risk of ICU admission and prolonged hospitalization in comparison to patients presenting with complications secondary to other causes (Table 3).

The variables assessed on bivariate analysis (maternal age, marital status, school education, and skin color/ethnicity) did not show any significantly increased estimated risk of a worse prognosis (maternal near miss event or death) (Table 4). Concerning obstetric conditions, the occurrence of one or more prior abortions and the history of previous uterine surgery were identified as protective factors against the occurrence of severe complications secondary to ectopic pregnancy (Table 5). Substandard care was shown to be the most common among more severe cases of maternal morbidity due to EP, being identified in 22.7% of MNM and MD cases versus 15% in PLTC, but this was not a significant difference (Table 5).

Multivariate analysis (Table 6) identified that, among the factors evaluated simultaneously, the presence of previous uterine scar and nonwhite skin color was independently associated with protection against severe complications secondary to ectopic pregnancy.

4. Discussion

To the best of our knowledge, this is the first analysis of EP according to the new WHO concepts of potentially life-threatening condition, maternal near miss, and maternal death, in a large well-defined sample of women, with prospective nationwide data collection.

Much has been discussed about the risk factors for the occurrence of complications and death due to ectopic pregnancy, such as nonwhite skin color, presence of previous disorders (particularly diabetes mellitus), unstable marital status, lower level of school education, nulliparity, history of prior ectopic pregnancy, and delay in care provision [5, 10, 11]. However, specifically for near miss events and ectopic pregnancy, this assessment does not exist. Determining the risk for severe clinical course may help in the management of these women. Despite all laboratory and imaging advances that permit early diagnosis and treatment, ectopic pregnancy is still an important cause of maternal death [2, 5]. The WHO estimates that 4% of all maternal deaths occurring in developed countries and 0.5% in developing settings are due to ectopic pregnancy [9, 12]. In our study, we found 0.7% (1/140) of deaths related to ectopic pregnancy, a proportion

Table 4: Estimated risk of worse outcome (MNM + MD) among maternal morbidity cases due to ectopic pregnancy according to some sociodemographic characteristics.

Characteristics	MNM + MD	PLTC	PR	95% CI
Age (years)				
10–19	11.5	6.6	1.83	0.78–4.27
20–29	46.2	52.1	(Ref.)	
30–39	34.6	36.0	1.08	0.37–3.15
40–49	7.7	5.2	1.58	0.31–8.08
(*n*.)	(26)	(286)		
Marital status (a)				
Married/cohabitating	55.6	46.9	1.38	0.49–3.88
Single/separated/widow	44.4	53.1	(Ref.)	
(*n*.)	(18)	(224)		
School education (b)				
Fundamental (primary)	47.1	42.8	(Ref.)	
Medium (high)	41.2	46.1	0.83	0.29–2.38
Superior (university)	11.8	11.2	0.96	0.17–5.34
(*n*.)	(17)	(152)		
Skin color/ethnicity (c)				
White	72.7	37.5	(Ref.)	
Nonwhite	27.3	62.5	0.26	0.05–1.32
(*n*.)	(22)	(192)		

MNM: maternal near miss; MD: maternal death; PLTC: potentially life-threatening condition; PR: prevalence ratio adjusted for cluster effect; 95% CI: 95% confidence interval for prevalence ratio. Missing values for (a) 70 cases; (b) 143; (c) 98.

lower than that observed in all developed countries. However, the number was close to the 0.5% observed in Latin America [9, 12]. Unfortunately, there are no comparative data for PLTC in the literature.

Specific mortality due to ectopic pregnancy alone does not fully describe obstetric care. Therefore, it is important to consider the health indicators described by the WHO in 2009 [15]. The maternal near miss incidence ratio and SMOR are aimed at estimating the complexity of care. Therefore, higher values meant that more women required high-complexity care. The MNM : MD ratio represents which proportion of near miss cases progressed to maternal death. The mortality index in turn represents an estimate of performance. Thus, when this index is high (higher than 20%), the quality of obstetric care provision for severe cases was not adequate [15, 17]. For the first time, these indicators recommended by the WHO have been described for ectopic pregnancy. Therefore, no results are available for comparison. Hopefully these figures will be worth for future comparisons with other population studies approaching maternal morbidity as the big one recently issued by the WHO [20].

The conditions of severe maternal morbidity related to ectopic pregnancy are associated with tubal rupture, rapid clinical deterioration due to major intra-abdominal bleeding, and posterior progression to hypovolemic shock, requiring blood transfusion [3, 10, 11]. Bleeding was actually the main diagnostic criteria used to identify PLTC cases in the current study. Furthermore, regarding conditions of severity management in patients with ectopic pregnancy, laparotomy and blood transfusion were the most important conditions. It is fundamental to consider that this study assessed a specific group of women with a severe condition. Cases in which an early diagnosis was made, allowing for clinical treatment with methotrexate or laparoscopic surgery, and unruptured EP in hemodynamically stable patients were not included in the current case study.

Another protective factor identified was history of prior abortion. According to Sindos et al., nulliparous patients tend to seek medical care earlier. As soon as these patients perceive any different symptoms such as pain or bleeding, they seek medical treatment and ectopic pregnancy is identified early, before tubal rupture [5]. The same association may be true for patients with a previous history of abortion [21]. Knowing the symptoms, these women would seek medical care sooner, which would allow an earlier diagnosis of ectopic pregnancy. This is a protective factor against the development of a more severe outcome associated with ectopic pregnancy. History of previous uterine surgery was also identified as a protective factor, possibly due to greater medical surveillance in these cases.

On multivariate analysis, apart from history of previous uterine surgery, we also found skin color as a protective factor, in contrast to descriptions in the literature reporting nonwhite skin color as a risk for the occurrence of complications and death from ectopic pregnancy. We should always bear in mind that the risk factors described are not related to near miss cases. There are still no comparative data for near miss cases in the literature and these cases may

Table 5: Estimated risk of worse outcome (MNM + MD) among maternal morbidity cases due to ectopic pregnancy according to some obstetric characteristics.

Characteristics	MNM + MD	PLTC	PR	95% CI
Previous abortions (a)				
None	95.7	66.8	(Ref.)	
1 or more	4.3	33.2	**0.10**	**0.01–0.78**
(*n*)	(23)	(271)		
Previous C-sections (b)				
None	86.4	76.9	(Ref.)	
1	9.1	18.1	0.47	0.11–2.01
2 or more	4.5	5.0	0.82	0.10–7.00
(*n*)	(22)	(260)		
Parity (c)				
0	37.5	35.8	(Ref.)	
1-2	45.8	48.3	0.91	0.34–2.45
≥3	16.7	15.9	1.00	0.29–3.52
(*n*)	(24)	(271)		
Previous uterine surgery (d)				
Yes	0.0	3.4	**<0.01**	**<0.01-<0.01**
No	100.0	96.6	(Ref.)	
(*n*)	(17)	(207)		
Gestational age at resolution (e)				
<9 weeks	71.4	73.2	(Ref.)	
≥9 weeks	28.6	26.8	1.09	0.32–3.64
(*n*)	(14)	(142)		
Substandard care—delays (f)				
Yes	22.7	15.0	1.59	0.55–4.57
No	77.3	85.0	(Ref.)	
(*n*)	(22)	(266)		

MNM: maternal near miss; MD: maternal death; PLTC: potentially life-threatening condition; PR: prevalence ratio adjusted for cluster effect; 95% CI: 95% confidence interval for prevalence ratio. Values in bold type indicate statistically significant values. Missing values for (a) 18 cases; (b) 30; (c) 17; (d) 88; (e) 156; and (f) 24 cases.

Table 6: Variables independently associated with a worse outcome (MNM + MD) among maternal morbidity cases due to ectopic pregnancy ($n = 187$).

Variable	Coefficient	SE coef.	*P*	PR_{adj} (95% CI)
Previous uterine scar	−22.65	0.71	**<0.001**	**<0.01(<0.01-<0.01)**
Skin color (nonwhite)	−1.84	0.87	**0.047**	**0.16 (0.03–0.97)**
Constant	−1.74	0.38	**<0.001**	

MNM: maternal near miss; MD: maternal death.

PR_{adj}: prevalence ratio adjusted for cluster effect and all remaining significant predictive factors.

Multiple Poisson regression, controlled by age (years); marital status (married/cohabitating: 1; others: 0); school education (up to high: 0; superior: 1); skin color (white: 0; nonwhite: 1); BMI (underweight/adequate: 0; overweight/obese: 1); previous abortion (0; ≥1 : 1); previous C-sections (0; ≥1: 1); parity (0; ≥1: 1); previous uterine scar (yes: 1; no: 0); gestational age at resolution (<9 weeks: 0; ≥9: 1); occurrence of substandard care delays (yes: 1; no: 0). Values in bold type indicate statistically significant values.

behave differently [5, 10, 11]. Furthermore, the widespread miscegenation of the Brazilian population might lead to some difficulty in clearly defining ethnicity.

One of the most interesting findings of the present study was information on the quality of care, with evidence of increased substandard care and/or delays in more severe cases. A similar suggestion was made by van Mello et al. in a case-control study, comparing EP patients developing complications after abdominal hemorrhage to hemodynamically stable EP patients. Those authors emphasized that since patient-related risk factors have not been consistent in identifying a worse outcome as yet, the key point would be to focus on awareness about EP and its clinical management [3]. Indirectly we could argue that the cases managed in places with better resources, easy access for women to health facility, and more trained health professionals had the ectopic pregnancy diagnosed earlier, before a severe complication developed, and these cases were managed clinically,

perhaps with laparoscopy or with methotrexate. These cases were not enrolled at all in the current study because they are not classified as severe morbidity.

Some possible limitations of this study must be considered. As a secondary analysis of a larger study, information about important risk factors usually assessed for EP cases was lacking, for example, previous EP (data collection concerned previous history of abortion), history of pelvic inflammatory disease, and history of infertility. There was also a lack of data on diagnostic tools used for each case: ultrasound findings and hCG levels or clinical findings at diagnosis.

5. Conclusions

A relatively large number of maternal morbidity cases due to EP were found in the Brazilian population during the surveillance period, raising awareness of this condition and its impact on female reproductive life. No important risk factors for increased severity were identified. However, there seems to be deficient or substandard care associated with complicated EP cases. Further action taken would be to address care providers to develop specific guidelines and interventions for the prevention of severe maternal morbidity due to this specific condition.

Conflict of Interests

The authors denied any conflict of interests.

Authors' Contribution

The idea for the study arose in a group discussion among all the authors. After the end of data collection, Edilberto Alves Rocha Filho, Danielly Scaranello Santana, Jose Guilherme Cecatti, and Maria Helena Sousa prepared a detailed plan of analysis which was then performed by Maria Helena Sousa. The first version of the paper was drafted by Edilberto Alves Rocha Filho and Danielly Scaranello Santana and then complemented with suggestions made by the other authors. Jose Guilherme Cecatti and Maria Laura Costa supervised the entire process. All authors contributed to the development of the study protocol and approved the final version of the paper.

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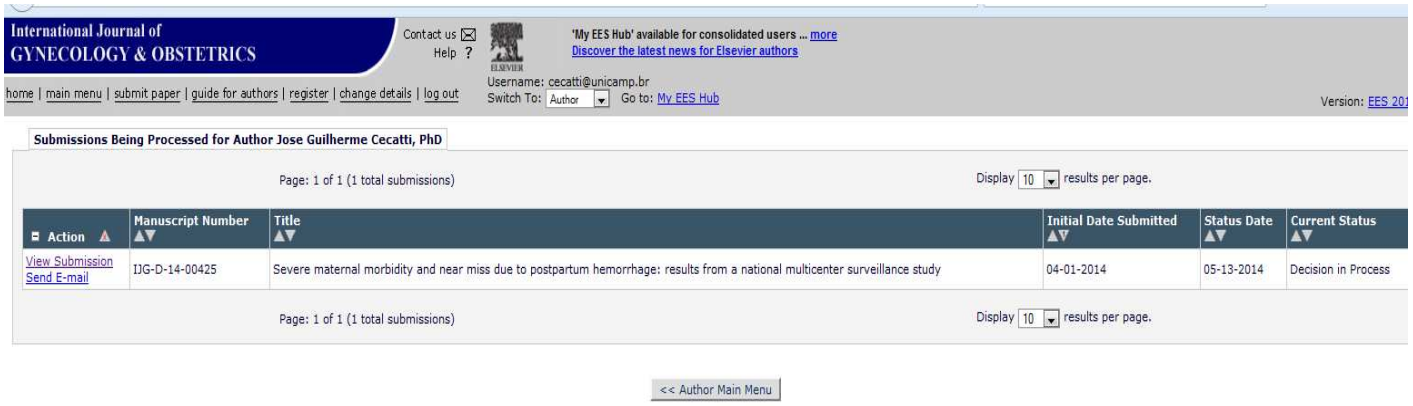
4.2. Artigo 2



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CLINICAL ARTICLE

Severe maternal morbidity and near miss due to postpartum hemorrhage: results from a national multicenter surveillance study

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Synopsis: severe maternal morbidity due to postpartum hemorrhage is frequent and the knowledge of it associated factors is worth for avoiding severe maternal outcomes

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ABSTRACT

Objective: to assess the occurrence of severe maternal complications due to postpartum hemorrhage (PPH) and its associated factors. *Method:* A multicenter cross-sectional study, with prospective surveillance of potentially life-threatening conditions (PLTC), near miss (MNM) and maternal death (MD). PPH complications, sociodemographic and obstetric characteristics and conditions of severity management were assessed, estimating prevalence ratios with their 95%CI. Factors independently associated with severe maternal outcome were identified using multiple regression analysis. *Results:* Among the 9.555 cases of severe maternal morbidity, 1192 (12.5%) had complications due to PPH: 981 PLTC, 181 MNM and 30 MD. Severe maternal outcome ratio (SMOR) was 2.6/1000LB among PPH cases and 8.5/1000 LB among other remaining causes. Cases of PPH had a higher risk of blood transfusion and return to the operating room, than those with complications from other causes. Maternal age, lower gestational age, a previous uterine scar, and delivery by C-section were the main factors associated with an increased risk of severe maternal outcome secondary to PPH. *Conclusion:* postpartum hemorrhage is a relatively frequent condition leading to severe maternal morbidity and the knowledge of factors associated with its severe maternal outcome (MNM+MD) could be useful for improving the quality of obstetric care and maternal outcomes.

Keywords: Postpartum hemorrhage; severe maternal morbidity; maternal near miss

1. Introduction

Postpartum hemorrhage (PPH) is a major concern worldwide and a leading cause of maternal morbidity and mortality, especially in low and middle income countries [1]. In these settings it is estimated that PPH is responsible for one fourth to one third of all maternal deaths [2,3]. For each of these deaths, around 20 women survive carrying along consequences of related morbidities [3], which represent a great social and economical burden.

The great majority of PPH cases are due to uterine atony, and key risk factors involve circumstances that over distend the uterus, labor induction and augmentation, previous cesarean delivery, hypertensive disorders of pregnancy, fibroids, placenta previa, and coagulopathy [4]. Several studies have shown an unexpected trend towards increasing PPH incidence over the last decade, even in high income countries, most likely due to multifactorial causes, including advanced maternal age, obesity, comorbidities, multiple pregnancy, ethnicity, and mainly rising cesarean section rates [5-8].

The definition of PPH is based on blood loss estimation during or within 24h of delivery [9]. This is challenging in clinical practice and usually the diagnosis is made by visual estimation of blood loss with most certainly under diagnosed situations [10,11]. This inaccuracy of blood loss estimation triggers every effort of determining PPH incidence worldwide (4) and has recently raised new possibilities of identifying clinical signs that could objectively relate to blood loss, such as the shock index [12]. Depending on pre-existing conditions such as anemia, the impact of an untreated PPH can lead to hypovolemic shock, multi-organ dysfunction and maternal death [13]. Timely and accurate identification is important to initiate appropriate interventions (including drugs, surgery, and referral) and improve outcome [14].

PPH has been extensively explored in scientific literature. However, few studies have undertaken consistent prospective data on severe maternal morbidity due to PPH. As a secondary analysis of a multicenter cross-sectional study for the surveillance of severe maternal morbidity in Brazil [15], the purpose of the current study is to appraise PPH, using the WHO concepts and criteria [16] of potentially life-threatening condition (PLTC), maternal near miss (MNM) and maternal death (MD). Diagnostic criteria for

the identification of the conditions, as well as socio-demographic and obstetric characteristics associated with a severe maternal outcome of PPH were explored.

2. Materials and methods

A national multicenter cross-sectional study was conducted in 27 Brazilian referral obstetric units in different geographical regions of the country. Over a 12-month period, from July 2009 to June 2010, a prospective surveillance of PLTC, MNM and MD was conducted, using the WHO criteria and classification [16-18]. Sample size was originally estimated in approximately 75.000 deliveries that should be under surveillance to identify near miss cases using those criteria.

Accordingly, all medical charts of women admitted to participating hospitals for delivery or for any problem related to pregnancy were reviewed immediately after hospital discharge. Medical records of women transferred to other healthcare units or of those who died were also reviewed. Information, when needed, was also obtained from other sources, such as prenatal record forms, or directly from the healthcare team in charge.

Data collection was performed in a specific form containing information about adequacy of health care and the occurrence of delays in receiving appropriate care. During data collection, the forms were filled. The data was then entered into electronic forms hosted in the project website, in the institutional web page of the coordinating center and sent to a central database, using the OpenClinica 3.0®, a specific platform for management of clinical studies. Further methodological details on the study are already published [15,19,20]. Approval from the IRB of each institution and from the National Council for Ethics in Research was obtained before the starting the study.

Quality control was systematically pursued. A manual of operation was developed and provided to all investigators and coordinators for training occurring before starting data collection. During the study, each local coordinator reviewed the forms, checked for errors and searched for missing data. The local investigator performed a new review to identify possible inconsistencies. Finally, the national study coordinators checked the database, identified possible inconsistencies and sent an error report to the participating centers which were required to respond and correct all information [19].

During the study, constant auditing with a set of validation and cross checking set of rules as part of an online data management, assigned a systematic evaluation of possible delays and deficiencies in the quality of care and health system inadequacy, with data on inter-hospital transfer, patient refusal in accepting treatment or lack of equipment or medication. Overall they were operationally defined as a substandard care. Hemorrhagic complications were systematically investigated and could include ante and intrapartum hemorrhage, PPH, complicated ectopic pregnancy or abortion or other severe hemorrhage (such as wound hematoma).

Initially cases were divided into obstetric complications due to PPH or due to any other cause. The prevalence of PLTC, MNM and MD was calculated and compared between these groups. Then the health indicators related to maternal morbidity and mortality were estimated: maternal near miss ratio (MNMR), severe maternal outcome ratio (SMOR=MNM+MD), maternal near miss to maternal death ratio (MNM:MD ratio), mortality index and maternal mortality ratio (MMR), according to WHO recommendations [16].

The criteria used for the identification of MNM and MD, as well as the conditions of severity management were assessed in these groups (PPH and other causes). The prevalence ratio adjusted for cluster effect of the design with their respective 95%CI for the conditions of severity management were estimated. The correction for the cluster effect of the design was used because each participating center was considered as a cluster, and the correspondent heterogeneity in each variable among clusters was adequate [20,21]. Sociodemographic and obstetric factors possibly associated with the occurrence of a severe maternal outcome among women with PPH were evaluated with prevalence ratio adjusted for cluster effect with their respective 95%CI, comparing women with PLTC and those with severe maternal outcome (MNM+MD). Finally, a multiple Poisson regression analysis was used to identify the factors independently associated with severe maternal outcome of complications due to PPH.

3. Results

In a total of 9,555 women identified with severe complications in pregnancy, delivery or postpartum period, a total of 8645 (90.5%) presented PLTC; 770 (8%) MNM and 140 (1.5%) MD. PPH accounted for the majority of hemorrhagic complications,

with 981 women identified with PLTC, 181 with MNM and 30 MD. Uterine atony was the most frequently diagnosed condition in this group. When reporting severe maternal outcome, MNM and MD, PPH was responsible respectively for 23.5% and 21.4% of the total cases in each group. PPH was responsible for 1192 cases (12.5%) with obstetric complications while 8363 (87.5%) were resulted from all other causes (Table 1, Figure 1).

The MNMR was 2.2/1000LB among PPH cases and 7.2/1000LB among the remaining causes; the SMOR was 2.6/1000LB among PPH cases and 8.5/1000LB among the remaining causes. The MNM:MD ratio was 6:1 for PPH cases and 5.4:1 for the remaining causes. The MMR was 36.5/100,000LB for PPH cases and 133.9/100,000LB for the remaining causes (Table 1). Among the severe maternal outcomes (MNM and MD), when applying the WHO criteria for identifying near miss events, the most widely used criteria for PPH was the management, present in 142 MNM cases (78.5%) and in all the 30 MD (Table 1).

Regarding conditions of severity management, patients who had PPH showed a higher risk of having blood transfusion and of returning to the operating room in comparison to patients with complications secondary to other causes (Table 2). On bivariate analysis, maternal age over 30 years old and specially over 40 years showed a significant higher risk of a worse prognosis for PPH cases. However, having a partner and a university level of schooling were both associated with a severe maternal outcome among PPH cases than those with a PLTC (Table 3).

Concerning obstetric conditions, history of previous C-section, one or more previous births, history of previous uterine scar, absent prenatal care, preterm delivery (between 28 and 36 weeks of gestation), admission in the postpartum period, prenatal care covered by health insurance, and current delivery by cesarean section, showed an increased estimated risk of severe maternal outcome for cases with PPH (Table 4).

Multivariate analysis (Table 5) identified that among the factors evaluated simultaneously, gestational age at admission below 37 weeks, maternal age, delivery by C-section and a previous uterine scar were all independently associated with a severe maternal outcome (near miss or maternal death) among cases of PPH comparatively with only PLTC. On the other hand, the history of a clinical condition previous to

pregnancy was significantly less frequent among PPH cases with a severe maternal outcome.

4. Discussion

PPH is a leading cause of mortality and morbidity worldwide and has been extensively studied in the last few decades, with great awareness towards its burden especially in low and middle income countries [7]. For many years, interest was focused on the evaluation of risk factors, prevention and treatment, with a great number of guidelines aiming timely approach [9]. Recently, studies have tried to understand reasons for substandard care considering PPH [8], accurate diagnosis [12] and identification of potentially severe cases. The new WHO concepts of and criteria for near miss were already used to evaluate this condition. Recently the published results of the WHO Multicountry Survey on Maternal and Newborn Health, a cross-sectional study implemented in 29 countries around the world, with surveillance of more than three hundred thousand delivering women, identified 2538 MNM and 486 MD. For this population, PPH was the most frequent obstetric complications identified among women with severe maternal outcome; followed by preeclampsia and eclampsia [1,22]. In our study, we had similar findings, with hemorrhage as the second most important complication identified and uterine atony as its main cause.

Most of the variables considered as related to increased risk of severity towards MNM and MD in PPH were in accordance to previous results in the literature, such as increasing maternal age, multiparaty, and previous cesarean section [1,4,22]. However, a few of our findings were unexpected, such as schooling at university level, having a partner and health insurance coverage of prenatal care associated with the severe maternal outcome. We were not able to find a previous similar finding already reported. However two points should be taken into account. First we are focusing only cases of PPH and assessing the risk of a worse outcome. We could not discard the situation that the worse outcome of PPH could be more the result of a limited timely intervention at health facility for women covered by health insurance (and married, higher education level, etc.), while the sample of public hospitals included in the study are mainly of big referral tertiary university hospitals which are supposed to provide good standard care.

Second, most risk factors already described are mainly related to maternal mortality or any kind of maternal morbidity generally defined, not exactly to near miss cases.

One of the most interesting findings of this study relates to the use of the near miss set of criteria in the identification of cases. Our results clearly demonstrate that for PPH, management criteria were the most important (such as massive blood transfusion and hysterectomy). That explains the difficulty to consider the accurate diagnosis of this complication in terms of blood loss quantification. Laboratory findings are not always timely accurate and clinical findings are yet to be adequately tested for obstetric population, especially in primary and secondary health settings. Almost certainly, the improvement for covering the gap of knowledge in the study of PPH would be the identification of early clinical signs to allow early diagnosis and timely treatment, especially in high risk population [12].

When comparing cases with postpartum hemorrhage and those with other causes of maternal morbidity regarding the criteria for severity management, those which appeared as significantly associated with PPH were blood transfusion and return to the operating room. These findings are obviously not surprising, as both interventions are specifically recommended for completing the standard procedures for management of severe PPH [9].

Specific mortality due to PPH alone does not fully describe obstetric care, its characteristics and quality. It is also worth to consider the health indicators recommended by the WHO. The maternal near miss incidence ratio and SMOR are meant to estimate the complexity of care. Consequently, higher values imply that more women require high-complexity care. They can have this care or not, depending on the availability of such resources and the access to them. Depending on this, the proportion of maternal deaths can be lower or higher. The MNM:MD ratio represents which proportion of all near miss cases progressed to maternal death. The higher this ratio, the better the quality of care the women received. The mortality index represents a performance estimate. Thus, when this index is high (higher than 20%), the quality of obstetric care provision for severe cases was not adequate [16,23]. For the first time, these indicators recommended by the WHO have been described for PPH. Therefore, no results are available for comparison. Hopefully these data will be worth for future

comparisons with other population studies approaching maternal morbidity due to postpartum hemorrhage as the WHO study [1].

There are of course some possible limitations of the current study that must be considered. As a secondary analysis of a larger study, information that could be of interest for the analysis of PPH, such as data on management of third stage of labor, use of different uterotonic drugs as prophylaxis, pre-labor hemoglobin level or blood loss estimation were not included the research clinical form and therefore those information could not be retrieved and assessed. However, this is one of a few analysis of PPH according to the new WHO concepts of potentially life-threatening condition, maternal near miss and maternal death, in a large well-defined sample of women, with a prospective nationwide data collection.

Finally the multiple analyses showed that the factors identified as independently associated with a severe maternal outcome among women experiencing a postpartum hemorrhage are generally those previously found, including the lower gestational age when the complication occurred, higher maternal age, delivery by a Cesarean section and a previous uterine scar. On the other hand, the existence of a risk or a pathological condition previous to pregnancy was negatively associated with a severe maternal outcome among these cases of PPH. We do not have the definitive explanation for that but we could hypothesize that those women identified as at higher risk for PPH received an obstetric care of better quality, thus avoiding the way to the worse outcome. This would certainly reinforce the recommendation of using the maternal near miss approach for the evaluation of quality of care [23]. Even more, the current study shows that any low and middle income setting is able to implement such a surveillance system in order to identify its main causes of morbidity and provide timely and adequate care to improve maternal outcomes.

Conflict of interests

The authors denied any conflicts of interests.

Authors' contributions

The idea for the study arose in a group discussion among all the authors. After the end of data collection, EARF, JGC and MHS prepared a detailed plan of analysis which was then performed by MHS. The first version of the manuscript was drafted by EARF and MLC, and then complemented with suggestions made by the other authors. JGC and MLC supervised the entire process. All authors contributed to the development of the study protocol and approved the final version of the manuscript.

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Table 1. Prevalence of types of hemorrhagic complications among women with maternal potentially life threatening conditions, near miss and maternal deaths and their correspondent health indicators. Criteria used for identification of cases of MNM and MD.

Type of Complication	PLTC	MNM	MD	MNMR (/1,000 LB)	MMR (/100.000 LB)	SMOR (/1,000 LB)	MNM:MD ratio
Hemorrhagic Complications	23.0	43.5	35.7	4.1	60.9	4.7	6.7
Ante and intrapartum hemorrhage	7.1	18.2	10.0	1.7	17.0	1.9	10.0
Postpartum hemorrhage	**11.3 (981)**	**23.5 (181)**	**21.4 (30)**	**2.2**	**36.5**	**2.6**	**6.0**
Uterine Atony	7.6	11.0	9.3	1.0	15.8	1.2	6.3
Retained Placenta	1.3	3.6	1.4	0.3	2.4	0.4	12.5
Lacerations of perineum, vagina or cervix	1.1	1.3	2.9	0.1	4.9	0.2	2.0
Coagulopathy	0.2	3.8	6.4	0.4	11.0	0.5	3.6
Uterine Inversion	<0.1	0.3	0.7	<0.1	1.2	<0.1	8.3
Other obstetrical cause	1.2	3.5	0.7	0.3	1.2	0.3	25.0
Complicated ectopic pregnancy	3.1	3.4	0.7	0.3	1.2	0.3	25.0
Severe hemorrhage due to abortion	1.3	2.2	2.1	0.2	3.7	0.2	5.4
Another severe hemorrhage	0.7	3.0	9.3	0.3	15.8	0.4	1.9
Other non-hemorrhagic complications	77.0	56.5	64.3	5.3	109.6	6.4	4.8
Total	8645	770	140	9555			
WHO criteria for NM and MD among cases of postpartum hemorrhage		**MNM**	**MD**				
Clinical		(99)	(28)				
Laboratory		(64)	(26)				
Management		(142)	(30)				
Total		**181**	**30**				

PLTC: Potentially Life Threatening Condition; MNM: Maternal Near Miss; MD: Maternal Death;
MNMR: Maternal Near Miss ratio; MMR: Maternal Mortality Ratio; SMOR: Severe Maternal Outcome Ratio;
LB: 82,144

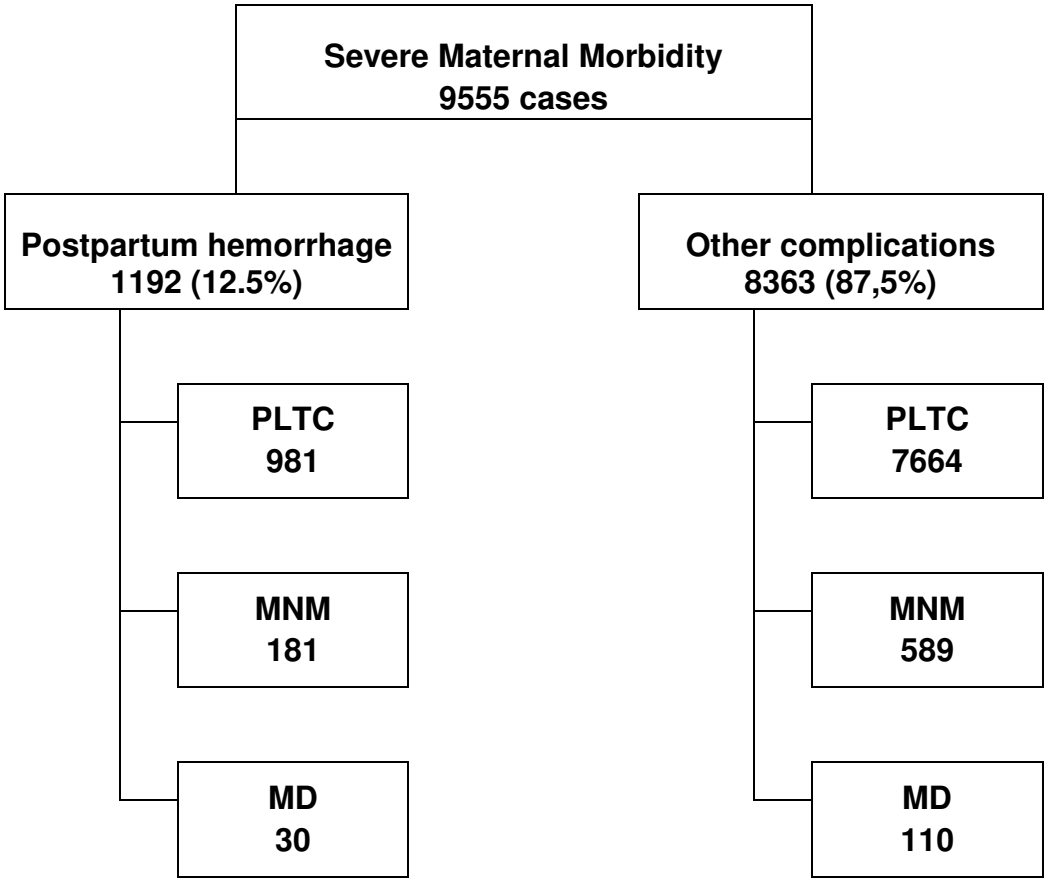

Figure 1. Flow of women with severe maternal morbidity due to postpartum hemorrhage or other causes according to the final outcome in PLTC (potentially life-threatening condition), MNM (maternal near miss) or MD (maternal death)

Table 2. Estimated risk of postpartum hemorrhage for several criteria for severity management among women with obstetrical complications

Criteria for Severity Management	Postpartum hemorrhage (%)	Other complications (%)	PR	95% CI
Blood transfusion	47.8	11.9	**4.02**	**1.74 – 9.28**
Central Venous Access	5.2	3.6	1.45	0.53 – 3.93
Admission to ICU	17.1	22.9	0.75	0.32 – 1.78
Prolonged hospital stay (>7 days)	18.9	31.6	0.60	0.26 – 1.37
Intubation not related to anesthesia	4.9	2.8	1.71	0.65 – 4.47
Return to operating room	13.5	1.9	**7.29**	**3.47 – 15.30**
Hysterectomy/laparotomy	10.1	5.6	1.80	0.68 – 4.77
Another major surgical procedure	1.4	0.7	2.13	0.96 – 4.73
Total	**(1,192)**	**(8,363)**		

PR: Prevalence Ratio adjusted for cluster effect; CI: Confidence Interval
Values in bold mean they are statistically significant

Table 3. Estimated risk of severe maternal outcome (SMO=MNM+ MD) among women with postpartum hemorrhage according to some socio demographic characteristics

Characteristics	SMO (%)	PLTC (%)	PR	95% CI
Age (years)				
10-19	12.8	20.0	0.85	0.53 – 1.35
20-29	39.8	51.4	(ref.)	
30-39	39.3	25.3	**1.76**	**1.28 – 2.41**
40-49	8.1	3.4	**2.38**	**1.31 – 4.32**
(n)	(211)	(981)		
Marital status (a)				
Married/with partner	68.6	51.1	**1.86**	**1.15 – 3.00**
Single/no partner/widow	31.4	48.9	(ref.)	
(n)	(172)	(874)		
Schooling (b)				
Primary	48.1	46.9	(ref.)	
High	36.6	46.1	0.80	0.56 – 1.14
University	15.3	7.0	**1.84**	**1.04 – 3.24**
(n)	(131)	(829)		
Ethnicity (c)				
White	58.5	66.8	(ref.)	
No White	41.5	33.2	1.34	0.68 – 2.63
(n)	(176)	(861)		
BMI (d)				
Low weight	25.6	17.1	1.21	0.63 – 2.31
Normal	36.6	30.3	(ref.)	
Overweight	19.5	28.0	0.61	0.32 – 1.17
Obese	18.3	24.6	0.65	0.34 – 1.24
(n)	(82)	(686)		

PLTC: Potentially Life Threatening Condition; MNM: Maternal Near Miss; MD: Maternal Death;
PR: Prevalence Ratio adjusted for cluster effect; CI: Confidence Interval
Missing values for: (a) 146 cases; (b) 232; (c) 155; (d) 424 cases
Values in bold mean they are statistically significant

Table 4. Estimated risk of severe maternal outcome (SMO=MNM+MD) among women with postpartum hemorrhage according to some obstetrical characteristics

Characteristics	SMO	PLTC	PR	95% CI
Previous abortions (a)				
None	78.8	78.6	(ref.)	
1 or more	21.2	21.4	0.99	0.69 – 1.42
(n)	(208)	(976)		
Previous C-sections (b)				
None	63.0	80.2	(ref.)	
1	20.5	16.0	**1.50**	**1.09 – 2.06**
2 or more	16.5	3.7	**3.41**	**1.92 – 6.04**
(n)	(200)	(962)		
Parity (a)				
0	31.7	44.8	(ref.)	
1-2	51.0	40.3	**1.62**	**1.25 – 2.09**
≥3	17.3	15.0	**1.51**	**1.04 – 2.18**
(n)	(208)	(976)		
Other previous uterine scar (c)				
Yes	3.6	0.7	**3.13**	**1.52 – 6.43**
Not	96.4	99.3	(ref.)	
(n)	(166)	(847)		
Number of prenatal visits (d)				
None	7.3	2.5	**2.22**	**1.27 – 3.89**
1-5	27.2	32.8	0.84	0.56 – 1.27
6 or more	65.6	64.6	(ref.)	
(n)	(151)	(868)		
Gestational age at admission (e)				
< 28 weeks	2.4	2.4	1.93	0.86 – 4.34
28-33	19.7	9.1	**3.43**	**1.53 – 7.68**
34-36	15.4	10.3	**2.62**	**1.22 – 5.64**
≥ 37	34.1	71.6	(ref.)	
Postpartum	28.4	6.7	**5.14**	**1.86 – 14.22**
(n)	(208)	(972)		
Previous clinical condition (f)				
Yes	42.7	53.2	0.70	0.41 – 1.20
Not	57.3	46.8	(ref.)	
(n)	(178)	(883)		
Mode of delivery (g)				
Vaginal	31.1	66.1	(ref.)	
C-section	68.9	33.9	**3.31**	**1.61 – 6.78**
(n)	(209)	(978)		
Coverage for prenatal care (h)				
Public	85.4	90.3	(ref.)	
Private	0.6	2.1	0.32	0.05 – 2.17
Health insurance	10.1	5.4	**1.69**	**1.07 – 2.68**
No prenatal care	3.9	2.2	1.63	0.90 – 2.96
(n)	(178)	(812)		

PLTC: Potentially Life Threatening Condition; MNM: Maternal Near Miss; MD: Maternal Death;
PR: Prevalence Ratio adjusted for the cluster effect; CI: Confidence Interval

Missing values for: (a) 8 cases; (b) 30; (c) 179; (d) 173; (e) 12; (f) 131; (g) 5; (h) 202 cases
Values in bold mean they are statistically significant

Table 5. Factors independently associated with severe maternal outcome (SMO=MD+MNM) among women with postpartum hemorrhage (n=970)

Factors	Coefficient	SE coef.	p	PR_{adj} [95% CI]
Gestational age at admission (<37 or postpartum)	1.09	0.26	<0.001	2.99 [1.76–5.07]
Age (years)	0.03	0.01	0.005	1.03 [1.01–1.06]
Mode of delivery (C-section)	0.84	0.29	0.008	2.31 [1.27–4.21]
Risk previous to pregnancy	-0.47	0.21	0.032	0.62 [0.40–0.96]
Previous uterine scar	0.94	0.43	0.036	2.57 [1.07–6.17]
Constant	-3.50	0.56	**<0.001**	

MD: maternal death; MNM: maternal near miss;
PR_{adj}: prevalence ratio adjusted for cluster effect and the other significant predictive factors.
Multiple Poisson regression, controlled by: Age (years); Marital status (married/with partner: 1; others: 0); Schooling (Up to high school: 0; University: 1); Skin color (white: 0; no white: 1); BMI (low weight/adequate: 0; overweight/obese: 1); Previous abortion (0; ≥1: 1); Previous C-sections (0; ≥1: 1); Parity (0; ≥1: 1); Previous uterine scar (yes: 1; no: 0); Number of prenatal visits (up to 5: 1; ≥6: 1); Gestational age at admission (<37 or postpartum: 1; ≥37: 0); Risk previous to pregnancy (yes: 1; no: 0); Mode of delivery (vaginal: 0/ C-section: 1); Coverage for prenatal care (public: 0/ other:1).

4.3. Artigo 3

From: susana.benedet@gu.se

To: cecatti@unicamp.br

Subject: Acta Obstetricia et Gynecologica Scandinavica (AOGS) - Manuscript ID AOGS-14-0367

Body: 03-May-2014

Dear Professor Cecatti:

Your manuscript entitled "Contribution of antepartum and intrapartum hemorrhage to the burden of maternal near miss and death in a national surveillance study" has been successfully submitted online and is presently being given full consideration for publication in Acta Obstetricia et Gynecologica Scandinavica (AOGS).

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Sincerely,
Acta Obstetricia et Gynecologica Scandinavica (AOGS) Editorial Office

Date Sent: 03-May-2014

MAIN RESEARCH ARTICLE

Contribution of antepartum and intrapartum hemorrhage to the burden of maternal near miss and death in a national surveillance study

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Running headline: antepartum hemorrhage and morbidity

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Conflict of interests

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

*Objective***:** to evaluate the occurrence of severe obstetric complications associated with antepartum and intrapartum hemorrhage among women from the Brazilian Network for Surveillance of Severe Maternal Morbidity. *Design***:** a multicenter cross-sectional study. *Setting*: 27 obstetric referral units in Brazil between July 2009 and June 2010. *Population*: 9,555 women categorized as having obstetric complications. *Methods*: The occurrence of potentially life-threatening conditions (PLTC), maternal near miss (MNM) and maternal deaths (MD) associated with antepartum and intrapartum hemorrhage was evaluated. Sociodemographic and obstetric characteristics and the use of criteria for management of severe bleeding were also assessed in these women. *Main outcome measures*: The prevalence ratios (PR) with their respective 95% confidence intervals adjusted for the cluster effect of the design, and multiple logistic regression analysis were performed to identify factors independently associated with the occurrence of severe maternal outcome (SMO). *Results***:** antepartum and intrapartum hemorrhage occurred in only 8% (767) of women experiencing any type of obstetric complication. However, it was responsible for 18.2% (140) of MNM and 10% (14) of MD cases. On multivariate analysis, maternal age and previous cesarean section were shown to be independently associated with an increased risk of severe maternal outcome (near miss or death). *Conclusion***:** SMO due to antepartum and intrapartum hemorrhage was highly prevalent among Brazilian women. Certain risk factors, maternal age and prior cesarean delivery in particular, were associated with the occurrence of bleeding.

Keywords:

Maternal near miss; obstetric complication; maternal death; maternal morbidity; antepartum hemorrhage; intrapartum hemorrhage; obstetric hemorrhage.

Abbreviations

AIH, antepartum and intrapartum hemorrhage; MD, maternal death; MNM, maternal near miss; PA, placental abruption; PLTC, potentially life-threatening conditions; PP, placenta previa; SMO, severe maternal outcome; WHO, World Health Organization.

Key message

Knowledge on hemorrhage as a cause of maternal morbidity and mortality is widely spread, however mainly for postpartum and not for antepartum and intrapartum conditions. We targeted their occurrence, risk factors and potential for preventability.

Introduction

Maternal mortality is directly related to maternal health conditions and maternal care in a region. Maternal mortality ratio is an important indicator of the quality of obstetric care. The situation is still critical in many populations worldwide, especially Southern Asia and sub-Saharan Africa. In these under-resourced regions, people have chronically lived with very high maternal mortality ratios that contribute to the elevated global rate of maternal deaths (1).

Advances in Obstetrics have significantly reduced maternal deaths resulting from hemorrhagic syndromes. Nevertheless, hemorrhage remains the leading cause of maternal deaths worldwide, accounting for around 50% of deaths in some low-income and middle-income countries. The reason for this high death rate is either the lack of adequate medical care or basic life support, despite the existence of well-defined protocols for prevention (2-4).

The aim of the fourth Millennium Development Goal is to decrease by 75% the maternal mortality ratio from 1990 to 2015 (5). Despite notable advances towards the improvement in mortality, it seems unlikely that this goal will be achieved. Although there has been a significant decrease in the number of maternal deaths – from virtually 47% between 1990 and 2010 – the declining rate is less than half of the rate necessary to attain such a goal. To make this possible, urgent interventions are required, including improved access to emergency obstetric services with staff qualified in labor care (1,5).

Antepartum and intrapartum hemorrhage (AIH) affects about 1% of all pregnancies and remains one of the leading causes of maternal and perinatal morbidity/mortality worldwide (6,7). About half of the cases are caused by placental abruption (PA) or placenta previa (PP). Uterine rupture, placental anomalies and local genital tract disorders, e.g. cervicitis and neoplasms are other causes of bleeding. No definitive cause is diagnosed in a reasonable amount of patients (8). AIH poses a great risk to the fetus, representing a major cause of perinatal mortality as well (9).

Intrapartum hemorrhage has various predisposing causes, e.g. vaginal laceration, uterine laceration during Cesarean section and placental accretism. Up to 90% of patients with placental accretism require transfusion therapy and maternal mortality is elevated (10). An increased risk of bleeding due to placenta accreta during delivery has

been observed even in high income countries and is related to the increase in Cesarean deliveries (11-13).

Despite a global improvement in maternal mortality rates, antepartum/intrapartum hemorrhage remains an important cause of maternal near miss (MNM). For every woman who dies, many more will survive but suffer from disabilities of any nature. Some of these conditions are less severe and may be characterized as Potentially Life-Threatening Conditions (PLTC). However, other conditions are quite severe and life-threatening, with characteristics very similar to cases that result in death (14,15). Maternal near miss is defined by the World Health Organization (WHO) as an event in which a woman almost died, but survived the complication during pregnancy, childbirth or within 42 days of termination of pregnancy. The woman had to present at least one criterion of severity as regarded to organ dysfunction or failure. For this purpose, standardized criteria were defined (clinical signs, laboratory-based or management-based) to identify near miss cases. These criteria were previously validated in a Brazilian obstetric population (16). The WHO also recommends that this approach should be used to evaluate the quality of obstetric care (17).

Characterization of maternal near miss morbidity is valuable for monitoring the quality of obstetric care. The use of maternal near miss as a model for the study of maternal death still offers considerable advantages. It allows the identification of risk factors and early signs of maternal life-threatening conditions. Furthermore, it has greater acceptance than maternal deaths with better performance of data analysis, since the near miss rate is higher than the death rate (16,18,19).

The present analysis proposed to evaluate the occurrence of factors associated with maternal complications (potentially life-threatening condition, maternal near miss and death) attributed to antepartum and intrapartum hemorrhage in a group of pregnant and postpartum women, included in the Brazilian Network for Surveillance of Severe Maternal Morbidity Study (16,20). The study was also aimed at identifying the sociodemographic and obstetric characteristics of women associated with a worse progression for severe maternal outcome (death or near miss), as well as the frequency of criteria for management of near miss cases among these women.

Method

The current study analyzed all hospital admissions for deliveries and postpartum care that occurred from July 2009 to June 2010 in 27 obstetric referral centers distributed in the five geographical Brazilian regions. Data was collected from the Brazilian Network for the Surveillance of Severe Maternal Morbidity (16,20) in a cross-sectional cohort study by prospective surveillance of patient charts at the time of hospital discharge. At each center, a local research coordinator collected data using manual forms. Data was then entered into an electronic on-line platform (OpenClinica® version 3.0 - Akaza Research, Waltham, MA, USA). Subsequently, data was checked and validated by the local investigator. Data quality control was performed at each participating center. Health professionals trained by the coordinating center made follow-up visits and analyzed randomly selected cases (about 5% of cases from each center). More detailed information about the methodological aspects of the study can be found in other publications (16,20).

Sample size was estimated at 75.000 deliveries that should be screened to obtain a sufficient number of maternal complications of diverse causes. Covering a total of 82.144 live births, the presence of any potentially life-threatening condition (PLTC), maternal near miss (MNM) and death (MD) was observed, according to new WHO definition and criteria (13). The sociodemographic, clinical, obstetric, prenatal characteristics, complications during labor and/or postpartum period, data on patient care and newborn conditions were analyzed in all included cases. The study was approved by the Institutional Review Board (IRB) of the study coordinating center, by the respective IRBs of each participating center, and finally by the National Research Ethics Council. The prevalence of different types of bleeding complications among women with PLTC, MNM and MD was calculated. The presence of criteria for management of severe bleeding was also evaluated among women with any type of antepartum or intrapartum hemorrhage and women who had some other complication, estimating the prevalence ratio (PR) and its respective confidence interval (95%CI). Similarly, the sociodemographic and obstetric characteristics of women with antepartum or intrapartum complications were analyzed, estimating the risk of severe maternal outcome (near miss or death). The presence of WHO criteria for near miss among

women with antepartum or intrapartum hemorrhagic complications was observed**.** The presence of factors associated with severe maternal outcome (SMO = MD + MNM) was also analyzed. Finally, multiple logistic regression analysis was carried out to identify factors independently associated with more severe complications due to antepartum or intrapartum hemorrhage.

The results were analyzed using SPSS® and EpiInfo®3.5.3 software packages. Values of $p<0.05$ were considered statistically significant. On bivariate analysis, a Fisher's exact or a chi-square test was used, estimating the PR with 95% CI adjusted for cluster effect of study design. For multivariate analysis, multiple Poisson regression including all the predictive variables in the model was used.

Results

During the study, 82.144 deliveries with live births were recorded in participating obstetric units. Of these, 9.555 women had some complication related to pregnancy, labor or the postpartum period, respectively with 8.645 (90.38%) PLTC cases, 770 (8.14%) of MNM and 140 (1.48%) of MD. Among women with PLTC, 23% had some bleeding complication, which also occurred in 43.5% of women with near miss events and 35.7% of those who died (Table 1). Antepartum and intrapartum bleeding complications accounted for 7.1% of PLTC cases, 18.2% of MNM cases and 10% of MD cases, representing 8% of all complications identified (Figure 1). Placental abruption was the most common cause in this category, accounting for 5.4% of PLTC cases, 9.2% of MNM cases and 5.0% of MD cases (Table 1).

Among the 140 women with near miss events and antepartum/ intrapartum hemorrhage, 73 had some clinical criteria, 45 had some laboratory-based criteria and 109 had some management-based criteria for near miss. In contrast, among the 14 deaths due to bleeding, 13 had some clinical criteria, 10 had some laboratory-based criteria and all 14 had some management-based criteria (Table 1).

Concerning criteria used for management of severe bleeding in women with antepartum and intrapartum hemorrhage compared to those with any other complications, a significantly higher risk was observed in this group for transfusion therapy (PR= 2.62), use of central venous access (PR= 1.62), return to the operating

room (PR= 1.57), and laparotomy or hysterectomy (PR= 2.18). A lower risk of using magnesium sulfate was also observed (PR=0.51) (Table 2).

The risk of severe maternal outcome (maternal near miss or death) was estimated among women with antepartum or intrapartum hemorrhage, in comparison to those presenting with any other obstetric complications, according to sociodemographic characteristics. The risk of SMO was higher in women from 30-39 years old (PR= 1.86) and in married women or those with a partner (PR=1.57) (Table 3). Among obstetric characteristics, the estimated risk of SMO was higher among women with a history of two or more previous Cesarean deliveries (PR= 3.23), increasing parity (PR= 2.87), hospital admission at a gestational age lower than 28 weeks (PR=1.74) or in the postpartum period (PR=4.69). The identification of any delay was only marginally associated with severe maternal outcome (OR 1.55, 95%CI 1.00-2.42) (Table 4).

Among all the factors evaluated together, multivariate analysis (Table 5) showed that higher age (PR= 1.03) and a previous history of Cesarean section (PR= 1.85) were independently associated with the occurrence of a more severe condition (near miss or death), due to complications resulting from antepartum and intrapartum hemorrhage.

Discussion

Despite advances in Obstetrics and Intensive Medicine, hemorrhage persists as the leading cause of maternal death. The important role of this condition in severe maternal morbidity and mortality was clearly evident in the current study. Bleeding complications were present in 23% of women who had any potentially life-threatening condition. However, when the most severe cases were analyzed – outcome categorized as near miss or death– hemorrhage was increasingly frequent (43.5% of near miss cases and 35.7% of deaths). Therefore, when a bleeding complication was present, clinical course tended to be more severe. Previous studies have already shown such an association (21,22).

Specifically, hemorrhage in the antepartum and intrapartum period was shown to be less frequent than postpartum hemorrhage, occurring in about one per cent of all live births (7). However, when the most severe cases were analyzed, its importance became more evident. Around 18% of all maternal near miss cases and 10% of all maternal deaths were due to these bleeding complications. Owing to their frequency, potential for preventability and crucial importance in maternal morbidity and mortality, healthcare

protocols and prevention policies are common in the prevention and treatment of postpartum hemorrhage. Nevertheless, the same does not occur for antepartum and intrapartum hemorrhage. Similar to postpartum hemorrhage, the majority of antepartum and intrapartum bleeding episodes are due to preventable causes. Due to its potential severity, special attention is required in this specific type of bleeding complication (1,2,23).

Placental abruption is the single most significant cause of antepartum hemorrhage. Although there are various known risk factors, the etiology and pathogenesis of the condition is multifactorial and not fully understood. Placental abruption is strongly associated with preeclampsia and this complication may account for up to 50% of cases. However, it may also be related to other causes, such as smoking and trauma (24-27). In this study, the high incidence and severity of this bleeding condition were shown. It was the leading cause of antepartum and intrapartum hemorrhage, accounting for 7.1% of near miss cases and 10% of all maternal deaths in the study. Placental abruption remains one of the most important causes of perinatal morbidity and mortality, although its rate is decreasing in some countries (7).

None of the WHO criteria for near misses were present in all the 140 near miss cases or all the 14 death cases, a fact that highlights the importance of systematically investigating these three types of criteria (clinical, laboratory-based and management-based) in any surveillance proposal, since none of them alone is able to identify all severe maternal outcomes.

It was not surprising that blood transfusion was used more frequently in women with antepartum/intrapartum hemorrhage than in the remaining complications. Transfusion therapy is expected in a hemorrhagic syndrome, since it is part of the treatment for this condition (28,29). However, this reinforces the importance of obstetric referral centers that are equipped with blood banks or blood centers. These blood units should be situated at a short distance from the delivery room and have the capacity to provide blood products expeditiously. Since this is one of the main lines of treatment in cases of severe complications, the lack or reduced availability of such blood banks, especially in locations far from large urban centers, may be related to the persistently high rates of

negative outcome related to hemorrhage. This could also be related to the marginal trend found of delays in obtaining care for the complication.

In addition to a greater need for central venous access, indicating the severity of the case, there was also a higher risk of returning to the operating room for more invasive surgical procedures, such as laparotomy or hysterectomy. The potential severity of antepartum and intrapartum hemorrhage was shown and contributed to explain the large amount of worse outcomes, e.g. maternal near miss and deaths, since these procedures potentiate the risk. Furthermore, maternity hospitals equipped with blood banks and trained staff members are required to perform these procedures, when necessary.

The increased risk of severe maternal outcome with increasing maternal age and parity is well-known. It is known that age and multiparity are also strongly associated with the occurrence of placental abruption and placenta percreta, along with various other morbid conditions during pregnancy and labor (24,25,26). The association between previous Cesarean sections and hemorrhage is also known. Among the possible explanations for this association are previous uterine scars that increase the risk of abnormal placentation and uterine rupture (12,13,30). In this study, a strong association was confirmed between prior Cesarean deliveries and bleeding. The risk of a worse outcome (near miss or death) due to antepartum and intrapartum hemorrhage was threefold, when there was a history of two or more prior Cesarean deliveries.

Women with gestational age below 28 weeks at hospital admission also had a higher risk of developing more severe outcomes (death or near miss) related to antepartum and intrapartum hemorrhage. Placental abruption and placenta percreta are major conditions responsible for these types of bleeding. These conditions are usually manifested at an early gestational age, which contributes to explain the increased risk found. Women in the postpartum period at the time of hospital admission also had a very high risk of developing a negative outcome. Because the study centers were obstetric referral centers, it was understood that these centers received patients who delivered in other healthcare services of lower complexity and had severe complications. An important reason for patient transfer is hemorrhage, due to the lack of blood banks in these services or the capacity to perform major surgery.

Of all factors related to antepartum and intrapartum hemorrhage presenting a high risk for more severe outcomes (near miss or death), multivariate analysis showed that maternal age and previous Cesarean section were independently significant. The importance of both factors in these bleeding complications was highlighted.

Conclusion

Antepartum and intrapartum hemorrhage were frequent causes of obstetric complications that had a direct relationship with more severe clinical outcomes (near miss or death). The presence of bleeding increased the risk of transfusion therapy significantly, along with the need for central venous access, return to the operating room and need to undergo puerperal hysterectomy. Advanced maternal age and a history of previous cesarean section were independently related to worse maternal outcomes associated with antepartum and intrapartum hemorrhage.

Author contributions

The idea for the study arose in a group discussion among all the authors. After the end of data collection, EARF, JGC and MHS prepared a detailed plan of analysis which was then performed by MHS. The first version of the manuscript was drafted by EARF and MLC, and then complemented with suggestions made by the other authors. JGC and MLC supervised the entire process. All authors contributed to the development of the study protocol and approved the final version of the manuscript.

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Legend for figure

Figure 1. Flowchart of women with severe maternal morbidity due to antepartum and intrapartum hemorrhage or other causes according to the final outcome in PLTC (potentially Life-threatening condition), MNM (maternal near miss) or MD (maternal death)

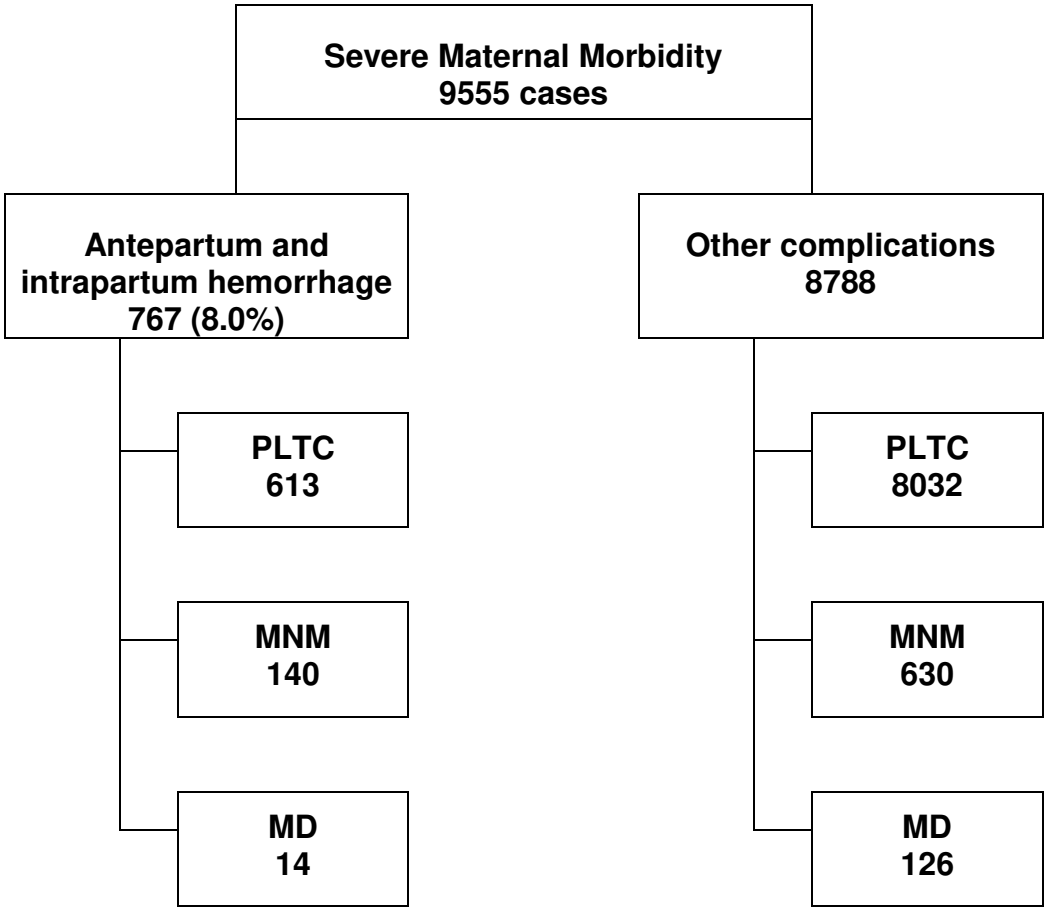

Table 1. Prevalence of the main causes of antepartum and intrapartum hemorrhage among maternal morbidity cases classified as potentially life-threatening conditions (PLTC), maternal near miss (MNM) and maternal death (MD)

Type of maternal morbidity	PLTC	MNM	MD	Total
Complications due to hemorrhage	23.0	43.5	35.7	
Antepartum and intrapartum hemorrhage	**7.1 (613)**	**18.2 (140)**	**10.0 (14)**	**(767)**
Placental abruption	5.4 (467)	9.2 (71)	5.0 (7)	(545)
Placenta previa/accreta	1.7 (147)	7.7 (59)	2.9 (4)	(210)
Uterine rupture	0.2 (17)	1.7 (13)	2.1 (3)	(33)
Other Complications (Total)	77.0 (8,645)	56.5 (770)	64.3 (140)	

WHO criteria for MNM and MD for antepartum and intrapartum hemorrhage	MNM	MD	Total
Clinical	(73)	(13)	(86)
Laboratory-based	(45)	(10)	(55)
Management-based	(109)	(14)	(123)
TOTAL	**140**	**14**	**154**

PLTC: Potentially Life-Threatening Condition; MNM: Maternal Near Miss; MD: Maternal Death.

Table 2. Estimated risk of antepartum and intrapartum hemorrhage in several criteria for management of severe bleeding in women with obstetric complications

Criteria for severity	Antepartum and intrapartum hemorrhage	Other complications	PR	95% CI
Blood transfusion	37.9	14.5	**2.62**	**2.01 – 3.40**
Central Venous Access	5.9	3.6	**1.62**	**1.01 – 2.60**
Admission to ICU	21.5	22.2	0.97	0.74 – 1.28
Prolonged hospital stay (>7 days)	31.6	29.9	1.06	0.94 – 1.19
Intubation unrelated to anesthesia	3.8	3.0	1.24	0.85 – 1.81
Return to operating room	5.0	3.2	**1.57**	**1.06 – 2.30**
Hysterectomy/laparotomy	12.3	5.6	**2.18**	**1.39 – 3.41**
Use of magnesium sulfate	25.8	50.3	**0.51**	**0.41 – 0.64**
Other major surgical procedure	1.2	0.7	1.61	0.83 – 3.13
Total	**(767)**	**(8,788)**		

PR: prevalence ratio adjusted for cluster effect; 95% CI: 95% confidence interval for prevalence ratio. Values in bold type are statistically significant

Table 3. Estimated risk of severe maternal outcome (SMO=MNM+ MD) among women with antepartum and intrapartum hemorrhage according to some sociodemographic characteristics

Characteristics	SMO	PLTC	PR	95% CI
Age (years)				
10-19	7.1	12.7	0.78	0.53 – 1.16
20-29	36.4	48.8	(ref.)	
30-39	51.9	31.5	**1.86**	**1.48 – 2.34**
40-49	4.5	7.0	0.89	0.48 – 1.63
(n)	(154)	(613)		
Marital status (a)				
Married/with partner	66.7	53.4	**1.57**	**1.02 – 2.42**
Single/no partner/widow	33.3	46.6	(ref.)	
(n)	(123)	(500)		
Schooling (b)				
Primary	52.0	51.0	(ref.)	
High	37.8	44.0	0.87	0.64 – 1.18
University	10.2	5.0	1.67	0.80 – 3.52
(n)	(98)	(402)		
Ethnicity (c)				
White	49.6	43.1	(ref.)	
Non White	50.4	56.9	0.81	0.40 – 1.64
(n)	(121)	(448)		

MNM: Maternal Near Miss; MD: Maternal Death; PLTC: Potentially Life-Threatening Condition.
PR: prevalence ratio; 95% CI PR: 95% confidence interval for prevalence ratio adjusted for cluster effect
Missing values for: (a) 144 cases; (b) 267; (c) 198; (d) 477 cases
Values in bold mean they are statistically significant

Table 4. Estimated risk of severe maternal outcome (SMO=MNM+MD) among women with antepartum and intrapartum hemorrhage according to some obstetric characteristics

Characteristics	SMO	PLTC	PR	95% CI
Previous abortions (a)				
None	71.7	75.7	(ref.)	
1 or higher	28.3	24.3	1.18	0.77 – 1.80
(n)	(152)	(609)		
Previous C-sections (b)				
None	53.5	74.0	(ref.)	
1	16.7	18.2	1.22	0.79 – 1.88
2 or higher	29.9	7.8	**3.23**	**2.12 – 4.90**
(n)	(144)	(599)		
Parity (a)				
0	19.1	38.9	(ref.)	
1-2	43.4	40.6	**1.93**	**1.31 – 2.85**
≥3	37.5	20.5	**2.87**	**1.93 – 4.27**
(n)	(152)	(609)		
A previous uterine scar (c)				
Yes	2.7	2.2	1.18	0.29 – 4.69
No	97.3	97.8	(ref.)	
(n)	(111)	(496)		
Number of prenatal visits (d)				
None	9.2	7.2	1.35	0.62 – 2.93
1-5	54.1	51.3	1.16	0.81 – 1.66
6 or more	36.7	41.6	(ref.)	
(n)	(98)	(433)		
Gestational age at admission (e)				
< 28 weeks	12.9	11.3	**1.74**	**1.01 – 2.99**
28-33	30.6	34.8	1.40	0.77 – 2.54
34-36	21.1	23.1	1.44	0.81 – 2.58
≥ 37	16.3	27.6	(ref.)	
Admission in postpartum	19.0	3.2	**4.69**	**2.59 – 8.48**

(n)	(147)	(597)		
Previous clinical condition (f)				
Yes	46.3	39.4	1.25	0.78 – 1.99
No	53.7	60.6	(ref.)	
(n)	(121)	(482)		
Mode of delivery (g)				
Vaginal	14.4	8.5	1.19	0.45 – 3.11
C-section	83.0	89.5	0.75	0.27 – 2.14
Still pregnant / Abortion/ EP	2.7	2.0	(ref.)	
(n)	(153)	(611)		
Onset of labor (h)				
Spontaneous	28.4	26.1	1.13	0.67 – 1.91
Induced	7.4	5.3	1.38	0.71 – 2.68
No labor/ Abortion/ Still pregnant	64.2	68.7	(ref.)	
(n)	(148)	(609)		
Coverage for prenatal care (i)				
Public	86.6	89.7	(ref.)	
Private	1.6	1.8	0.94	0.34 – 2.58
Health insurance	6.3	3.1	1.71	0.90 – 3.27
No prenatal care	5.5	5.5	1.03	0.49 – 2.16
(n)	(127)	(455)		
Occurrence of delays (j)				
Yes	32.2	21.1	1.55	1.00 – 2.42
No	67.8	78.9	(ref.)	
(n)	(146)	(554)		
Previous maternal conditions (k)				
Chronic hypertension	14.0	11.2	1.22	0.77 – 1.94
Smoking	11.6	9.5	1.18	0.54 – 2.62
Obesity	11.6	16.4	0.72	0.41 – 1.25
Drug addiction	4.1	1.9	1.81	0.90 – 3.67
(n)	(121)	(482)		

MNM: Maternal Near Miss; MD: Maternal Death; PLTC: Potentially Life-Threatening Condition.
PR: prevalence ratio; 95% CI PR: 95% confidence interval for prevalence ratio adjusted for cluster effect
Missing values for: (a) 6 cases; (b) 24; (c) 160; (d) 236; (e) 23; (f) 164; (g) 3; (h) 10; (i) 185; (j) 67; (k) 164 cases. Values in bold mean they are statistically significant

Table 5: Factors independently associated with severe maternal outcome (SMO=MD+MNM) among women with antepartum and intrapartum hemorrhage [n=743]

Variable	Coefficient	SE coef.	p	PR_{adj} [95% CI]
Age (years)	0.03	0.01	**0.001**	**1.03 [1.01–1.04]**
Previous C-sections (≥1)	0.61	0.18	**0.002**	**1.85 [1.28–2.66]**
Constant	-2.67	0.22	**0.001**	

MNM: maternal near miss; MD: maternal death; SMO: severe maternal outcome
PR_{adj}: prevalence ratio adjusted for cluster effect and other significant predictive factors.
Multiple Poisson regression, controlled by: Age (years); Marital status (married/with partner: 1; others: 0); Schooling (Up to high school: 0; University: 1); Ethnicity (white: 0; nonwhite: 1); BMI (underweight/adequate: 0; overweight/obese: 1); Previous abortion (0; ≥1: 1); Previous C-sections (0; ≥1: 1); Parity (0; ≥1: 1); Previous uterine scar (yes: 1; no: 0); Number of prenatal visits (up to 5: 1; ≥6: 1); Gestational age at admission (<37 or still pregnant: 1; ≥37: 0); Risk previous to pregnancy (yes: 1; no: 0); Mode of delivery (vaginal, cesarean: 1; Still pregnant/abortion/ectopic pregnancy: 0); Onset of labor (Spontaneous/induced: 1; No labor /abortion/still pregnant: 0); Coverage for prenatal care (public: 0/ other:1); Occurrence of delays) (Yes: 1; No: 0); Previous maternal conditions: Chronic Hypertension (Yes: 1; no: 0); Smoking (Yes: 1; no: 0); Obesity (Yes: 1; no: 0); Drug addiction (yes: 1; no: 0).

5. Discussão Geral

Apesar dos avanços tecnológicos na medicina, as hemorragias persistem como causa importante de óbito materno. A importância desta condição para a morbidade materna grave e a mortalidade mostrou-se evidente no presente estudo. As complicações hemorrágicas estavam presentes em 23% das mulheres que apresentaram alguma condição potencialmente ameaçadora da vida. E quando se analisaram os casos mais graves - desfechos em *near miss* ou óbito – sua frequência mostrou-se bem maior (43,5% dos casos de near miss e de 35,7% dos óbitos). Assim, quando uma complicação hemorrágica esteve presente, o quadro clínico tendeu a ser mais grave. Estudos anteriores já evidenciaram tal associação (Su & Chong, 2012; Alexander & Wortman, 2013).

HPP é uma das principais causas de mortalidade e morbidade materna no mundo inteiro e tem sido amplamente estudada nas últimas décadas, com uma maior conscientização para a sua importância, especialmente em países de baixa e média renda (Kramer et al., 2011). Por muitos anos, o interesse esteve focado na avaliação de fatores de risco, prevenção e tratamento, com um grande número de diretrizes visando abordagem oportuna (WHO, 2012). Recentemente, estudos têm tentado compreender as razões para os cuidados insuficientes envolvendo a HPP (Briley et al., 2014), a realização de diagnósticos precisos (Pacagnella et al., 2013) e a identificação dos casos potencialmente graves.

Os novos conceitos e critérios de near miss da OMS já foram utilizados para avaliar esta condição. Os resultados publicados no *Multicountry Survey on Maternal and Newborn Health*, um estudo transversal implementado em 29 países ao redor do mundo, com a vigilância de mais de trezentos mil mulheres

em trabalho de parto, recentemente identificou 2.538 casos de NMM e 486 MM. Para esta população, HPP foi a complicação obstétrica mais frequentemente identificada entre as mulheres com resultado materno grave, seguido de pré-eclâmpsia e eclâmpsia (Souza et al., 2013; Pacagnella et al., 2013). Em nosso estudo, tivemos resultados semelhantes, com a hemorragia como a segunda complicação mais importante identificada e atonia uterina como sua principal causa.

A hemorragia no período anteparto e intraparto mostrou-se menos frequente do que a hemorragia pós-parto, ocorrendo, como esperado, em cerca de um por cento de todos os nascimentos (Giordano et al., 2010). No entanto, quando foram analisados os casos mais graves, a sua importância tornou-se mais evidente. Cerca de 18% de todos os casos de near miss materno e 10% de todas as mortes maternas foram devido a estas complicações hemorrágicas. Devido à sua frequência, potencial de evitabilidade e crucial importância na morbidade e mortalidade materna, os protocolos de saúde e as políticas de prevenção são comuns na prevenção e tratamento da hemorragia pós-parto. No entanto, o mesmo não ocorre para hemorragias ante e intraparto. Semelhante à HPP, a maioria dos episódios de sangramento ante e intraparto é devida a causas evitáveis. Por sua gravidade potencial, é necessária uma atenção especial neste tipo específico de complicação hemorrágica (WHO, 2012; Morikawa et al., 2014).

O DPP é a causa mais importante de hemorragia anteparto. Embora existam vários fatores de risco conhecidos, a etiologia e patogenia da doença são multifatoriais e não totalmente compreendidas. O DPP é fortemente associado com pré-eclâmpsia e esta complicação pode ser responsável por até 50% dos casos. No entanto, também pode estar relacionada a outras causas, como tabagismo e trauma (Boisramé et al., 2014; Cheng et al., 2012; Tikkanen, 2011; Tikkanen et al., 2013). Neste estudo, foram mostradas as elevadas incidência e gravidade desta condição de sangramento. Foi a principal causa de HAI, o que representa 7,1% dos casos de near miss e 10% de todas as mortes maternas no estudo. O descolamento prematuro da placenta continua sendo

uma das mais importantes causas de morbidade e mortalidade perinatal, embora sua taxa esteja diminuindo em alguns países (Giordano et al., 2010).

Esta foi a primeira análise de gravidez ectópica já realizada de acordo com os novos conceitos da OMS de CPAV, NMM e MM em uma grande amostra bem definida de mulheres, com coleta de dados prospectiva e de âmbito nacional. Muito se têm discutido sobre os fatores de risco para a ocorrência de complicações e morte devido a gravidez ectópica, tais como a cor da pele não branca, presença de distúrbios anteriores (particularmente diabetes mellitus), estado civil solteira, menor nível de educação escolar, nuliparidade, história de gravidez ectópica anterior e atraso na prestação de cuidados (Sindos et al., 2009; Noell, 2011; Stulberg et al., 2011). No entanto, especificamente para eventos de near miss e gravidez ectópica, não existe ainda esta avaliação. Determinar o risco de curso clínico grave pode ajudar no manejo dessas mulheres.

Apesar de todos os avanços laboratoriais e de imagem que permitem o diagnóstico precoce e tratamento, gravidez ectópica ainda é uma causa importante de morte materna (Agdi & Tulandi, 2009; Sindos et al., 2009). A OMS estima que 4% de todas as mortes maternas que ocorrem nos países desenvolvidos e 0,5% das que ocorrem em países em desenvolvimento são devidas à gravidez ectópica (Khan et al., 2006; UNDP, 2005). Em nosso estudo, encontramos 0,7% (1/140) das mortes relacionadas com a GE, uma proporção menor do que a observada em todos os países desenvolvidos. No entanto, o número é próximo aos 0,5% observados na América Latina (Khan et al., 2006; UNDP, 2005). Infelizmente, não há dados comparativos para CPAV na literatura.

A maioria das variáveis consideradas como relacionadas ao aumento do risco de gravidade para NMM e MM na HPP estava de acordo com os resultados anteriores da literatura, como o aumento da idade materna, multiparidade e cesariana anterior (Souza et al., 2013; Oyelese & Ananth, 2010; Sheldon et al., 2014). No entanto, alguns de nossos resultados foram inesperados, como a escolaridade de nível universitário, ter um parceiro e

cobertura de seguro de saúde do pré-natal associados com um resultado materno mais grave. No entanto dois pontos devem ser levados em conta. Primeiro, focando apenas os casos de HPP e o risco de um resultado pior, não poderíamos descartar a situação que mesmo mulheres cobertas por um seguro de saúde (e casada, nível superior de escolaridade, etc) seriam direcionadas aos hospitais públicos incluídos no estudo, que são principalmente de grandes hospitais universitários terciários de referência e que deveriam prestar um bom atendimento padrão. Em segundo lugar, a maioria dos fatores de risco já descritos está principalmente relacionada com a mortalidade materna ou qualquer tipo de morbidade materna, não exatamente casos de near miss.

Um dos achados mais interessantes deste estudo refere-se à utilização de critérios de near miss para a identificação de casos. Nossos resultados demonstram claramente que para HPP, critérios de manejo foram os mais importantes (como transfusão maciça de sangue e histerectomia). Isso explica a dificuldade de considerar o diagnóstico preciso desta complicação em termos da quantificação de perda sanguínea. Os achados laboratoriais nem sempre são precisos e oportunos e os achados clínicos ainda estão para ser devidamente testados para a população obstétrica, especialmente em serviços primários e secundários de saúde. Quase certamente, a melhoria para cobrir a lacuna de conhecimento no estudo da HPP seria a identificação de sinais clínicos iniciais para permitir o diagnóstico precoce e tratamento oportuno, especialmente na população de alto risco (Pacgnella et al., 2013).

Já entre as mulhers com HAI, é interessante notar que em nenhum dos 140 casos de near miss e nos 14 casos de óbitos, foram observados de forma conjunta os três tipos de critérios para near miss da WHO (clínico, laboratorial ou de manejo).. Isso ressalta a importância de que estes três tipos de critérios devem sempre ser investigados e de que nenhum deles, isoladamente, é capaz de identificar todos os desfechos maternos graves. Nestas mulheres, igualmente, a transfusão sanguínea foi bem mais frequente do que nas demais complicações. Isso não é de se estranhar. Terapêutica transfusional é esperada em uma síndrome hemorrágica, uma vez que faz parte do tratamento para essa

condição (Bonnet et al., 2011; Gasim et al., 2013). No entanto, isso reforça a importância dos centros de referência obstétrica estarem equipados com bancos de sangue ou hemocentros. Estas unidades transfusionais devem ser situadas a uma curta distância da sala de parto e ter a capacidade de fornecer rapidamente produtos de sangue. Uma vez que esta é uma das principais linhas de tratamento em casos de complicações graves, a falta ou a redução da disponibilidade de tais bancos de sangue, especialmente em locais distantes dos grandes centros urbanos, pode estar relacionada com a persistência de elevadas taxas de resultado grave relacionadas à hemorragia. Isso também pode estar relacionado com a tendência encontrada de atrasos na obtenção de cuidados para a complicação. Além de uma maior necessidade de acesso venoso central, indicando a gravidade do caso, houve também um maior risco de retorno para a sala de cirurgia para procedimentos cirúrgicos mais invasivos, como a laparotomia ou histerectomia, o que sem dúvida agrava o risco relacionado à HAI.

As condições de morbidade materna grave relacionadas com a gravidez ectópica estão associadas à ruptura tubária, deterioração clínica rápida devido à hemorragia intra-abdominal de grande porte e progressão posterior ao choque hipovolêmico, necessitando de transfusão de sangue (Van Mello et al., 2012; Noell, 2012; Stulberg et al., 2011). O sangramento foi realmente um dos principais critérios diagnósticos utilizados para identificar os casos de CPAV entre as mulheres com gravidez ectópica. Além disso, laparotomia e transfusão de sangue foram as condições de manejo mais importantes. É fundamental considerar que este estudo avaliou um grupo específico de mulheres com uma condição grave. Casos em que um diagnóstico precoce foi feito, permitindo o tratamento clínico com metotrexate ou cirurgia laparoscópica em GE não rota em pacientes hemodinamicamente estáveis não foram incluídos no estudo atual. Um interessante achado deste estudo foram os dados sobre a qualidade do atendimento, com evidências de aumento de cuidados insuficientes e/ou demoras no atendimento na maioria dos casos graves relacionados à gravidez ectópica. Uma associação semelhante foi feita por Van Mello et al. (2012) em

um estudo caso-controle, comparando pacientes com gravidez ectópica que desenvolveram complicações após hemorragia abdominal com pacientes hemodinamicamente estáveis. Esses autores enfatizaram que, quando os fatores de risco relacionados a estas pacientes não eram consistentemente identificados, o resultado era um pior desfecho. Assim, o ponto chave seria focar a conscientização sobre GE e seu manejo clínico (Van Mello et al., 2012). Indiretamente pode-se argumentar que os casos tratados em locais com melhores recursos, de fácil acesso das mulheres à unidade de saúde e profissionais de saúde mais qualificados, tiveram a gravidez ectópica diagnosticada mais cedo, antes de uma grave complicação, e estes casos foram manejados clinicamente, talvez com a laparoscopia ou com metotrexato. Estes casos, no entanto, não foram contemplados no estudo atual porque eles não são classificados como morbidade grave.

O risco aumentado de desfecho materno grave com o aumento da idade materna e paridade entre mulheres com HAI, como encontrado, é conhecido. Sabe-se que a idade e a multiparidade estão fortemente associadas com a ocorrência de DPP e PP (Boisramé et al., 2014; Cheng et al., 2012; Tikkanen, 2011). O mesmo ocorreu entre cesarianas prévias e HAI. Dentre as explicações possíveis para esta última associação, sabe-se que incisões uterinas anteriores aumentam o risco de placentação anormal e de rotura uterina (Marshall et al., 2011; Say et al., 2009; Vogel et al., 2014). Verificou-se um risco 3 vezes maior de se ter um pior desfecho (*near miss* ou óbito) por hemorragia ante e intraparto quando existia história de duas ou mais cesáreas prévias. As mulheres com idade gestacional inferior a 28 semanas apresentaram risco elevado para a ocorrência de desfechos mais graves relacionados com hemorragias ante e intraparto. O DPP e a PP, principais responsáveis por estes tipos de hemorragia, muitas vezes estão presentes em idades gestacionais precoces, o que ajuda a explicar o risco aumentado nestas mulheres. As que já eram puérperas no momento da internação hospitalar, igualmente apresentaram risco bastante elevado para um desfecho negativo relacionado à HAI. Por serem de referência obstétrica os centros envolvidos no estudo, compreende-se que

estes recebam as pacientes que tiveram parto em outro serviços de menor complexidade e que apresentaram complicações graves, incluindo aí pacientes com esta condição.

Mortalidade específica por si só não descreve totalmente cuidados obstétricos, as suas características e qualidade. Também vale a pena considerar os indicadores de saúde recomendados pela OMS. A razão de near miss materno (MNMR) e SMOR servem para estimar a complexidade do atendimento. Consequentemente, valores mais altos significam que há mais mulheres precisando de atendimento de alta complexidade. Elas podem ter esse cuidado ou não, dependendo da disponibilidade de tais recursos e o acesso a eles. Dependendo disso, a proporção de mortes maternas pode ser inferior ou superior. A relação NMM:MM representa que a razão de quantos casos de near miss ocorreram para cada morte materna. Quanto maior esse índice, melhor a qualidade do atendimento que as mulheres receberam. O índice de mortalidade representa uma estimativa do desempenho. Assim, quando esse índice é elevado (superior a 20%), a qualidade da prestação de cuidados obstétricos para os casos graves não é considerada adequada (Say et al., 2009; WHO, 2013). Pela primeira vez estes indicadores recomendados pela OMS form descritos para a HPP. Portanto, não há resultados disponíveis para comparação. Esperemos que estes dados possam servir para futuras comparações com outros estudos populacionais.

A análise múltipla mostrou que os fatores identificados como associados de forma independente com um resultado materno grave entre as mulheres que experimentaram uma HPP são geralmente aqueles previamente encontrados, incluindo a idade gestacional menor quando a complicação ocorreu, maior idade materna, parto por cesariana e cicatriz uterina prévia.

Entre todos os fatores relacionados à HAI que foram relacionados a um risco elevado para os resultados mais graves, a análise multivariada mostrou que a idade materna e cesariana anterior foram independentemente significativos. A importância dos dois fatores nestas complicações hemorrágicas foi destacada.

Há, naturalmente, algumas possíveis limitações do estudo atual que devem ser consideradas. Como uma análise secundária, maiores informações que poderiam ser úteis na análise das hemorragias, tais como dados sobre o manejo da terceira fase do parto, uso de diferentes drogas uterotônicas como profilaxia, o nível de hemoglobina ou perda sanguínea estimada, não foram incluídas e, portanto, essas informações não puderam ser recuperadas e avaliadas. No entanto, esta é uma das poucas análises da HPP, HAI e GE de acordo com os novos conceitos da OMS de condição potencialmente ameaçadora da vida, near miss materno e óbito materno, em uma grande e bem definida amostra de mulheres, com coleta de dados prospectivos, de âmbito nacional.

Este estudo evidenciou o quão importante as SHO permanecem para a morbidade grave e para a mortalidade materna no Brasil, particularmente as hemorragias ante, intra e pós-parto. Perecebe-se que um fator preponderante para a assistência a estas mulheres com morbidade grave e consequentemente a redução dos óbitos, dado o alto índice de hemotransfusões e de retorno à sala cirúrgica e histerectomia/laparotomia, é uma rede hospitalar adequada, capilarizada, com suporte transfusional eficiente e estrutura com complexidade (tanto física como de pessoal) para grandes procedimentos cirúrgicos, o que infelizmente não corresponde à nossa realidade, principalmente nas regiões mais afastadas dos grandes centros.

6. Conclusões

1- Um número relativamente grande de casos de morbidade materna grave devido a gravidez ectópica foi encontrado na população brasileira durante o período de vigilância, o que eleva a sensibilização para esta condição e seu impacto sobre a vida reprodutiva das mulheres. Os fatores associados a um melhor resultado foram uma cicatriz uterina prévia e ser não branca. No entanto, parece haver cuidado deficiente ou demora associados a casos complicados de gravidez ectópica.

2- Hemorragia pós-parto persiste como uma das principais complicações obstétricas e como causa importante de morbidade materna grave e de óbito materno no Brasil. É elevada a frequência do near miss materno causado pela hemorragia pós-parto. Mostrou-se evidente a influência da idade materna elevada, da presença de cesarianas prévias, da multiparidade, da presença de cicatriz uterina prévia, da ausência de pré-natal, do parto por cesariana e da prematuridade no aumento substancial do risco de desenvolvimento de complicações obstétricas graves (near miss e óbito) em pacientes que apresentaram hemorragia pós-parto.

3- As hemorragias ante e intraparto foram causas frequentes de complicações obstétricas e estiveram diretamente relacionadas a desfechos clínicos mais graves (*near miss* ou óbito). A presença destas hemorragias aumentou significativamente o risco de hemotransfusões, necessidade de acesso venoso central, de retorno à sala cirúrgica e à necessidade de histerectomia puerperal. A idade materna elevada e a história de cesariana prévia foram independentemente relacionados a piores desfechos maternos relacionados às hemorragias ante e intraparto.

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8. Anexos

Anexo 1 – Formulário de Coleta Manual da Rede Nacional de Vigilância

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
[ ] 2 parto vaginal operatório
[ ] 3 parto cesárea antes do início do trabalho de parto
[ ] 4 parto cesárea após o início do trabalho de parto
[ ] 5 aborto
[ ] 6 prenhez ectópica
[ ] 7 continua grávida
[ ] 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
[ ] 2 placenta prévia/acreta/increta/percreta
[ ] 3 prenhez ectópica complicada
[ ] 4 rotura uterina
[ ] 5 hemorragia grave por aborto
[ ] 6 hemorragia pós parto
[ ] 7 outra hemorragia grave
[ ] 8 não houve/não consta
47. Se HEMORRAGIA PÓS- PARTO, especifique:
[ ] 1 atonia [ ] 2 retenção placentária [ ] 3 lacerações de trajeto [ ] 4 coagulopatia [ ] 5 inversão uterina [ ] 6 outra causa obstétrica

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

49. Qual complicação hipertensiva ocorreu no período?*

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

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

51. Quais complicações?*

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

52. Se SEPSE GRAVE, especifique o foco:

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

53. Se outro foco, especifique:_____

54. A mulher apresentou alguma das condições de manejo de gravidade?*
[ ] 1 sim [ ] 2 não [ ] 8 não consta

55. Quais condições estavam presentes?*

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

58. A mulher apresentou algum dos critérios laboratoriais de near miss?*
[ ] 1 sim [ ] 2 não [ ] 8 não consta

59. Se SIM, indique quais*:

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

60. A mulher apresentou algum dos critérios de manejo?*
[ ] 1 sim [ ] 2 não [ ] 8 não consta

61. Se SIM, indique quais*:

[ ] 1 uso de droga vasoativa contínua
[ ] 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: [ ]

Anexo 2 – 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: N° 097/2009 (Este n° deve ser citado nas correspondências referente a este projeto)
CAAE: 0071.1.146.000-09

I - IDENTIFICAÇÃO:

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

II - OBJETIVOS

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

III - SUMÁRIO

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

IV - COMENTÁRIOS DOS RELATORES

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

V - PARECER DO CEP

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

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

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

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

VI - INFORMAÇÕES COMPLEMENTARES

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

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

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

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

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

VI I- DATA DA REUNIÃO

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

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

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