UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

TESE DE DOUTORADO

IMPACTO DO RASTREAMENTO DO DIABETES MELLITUS GESTACIONAL SEGUNDO OS CRITÉRIOS DA ASSOCIAÇÃO INTERNACIONAL DE GRUPOS DE ESTUDO EM DIABETES E GRAVIDEZ

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SUMÁRIO

ABREVIATURAS E SIGLAS

ADA	*American Diabetes Association*
ADIPS	*Australian Diabetes in Pregnancy Society*
DMG	Diabetes mellitus gestacional
EBDG	Estudo Brasileiro de Diabetes Gestacional
GIG	Grande para a idade gestacional
GRADE	*Grading of Recommendations Assessment, Development and Evaluation*
HAPO	*Hyperglycemia and adverse pregnancy outcomes*
IADPSG	Associação Internacional de Grupos de Estudo em Diabetes e Gravidez (*International Association of Diabetes and Pregnancy Study Group)*
IC	Intervalo de confiança
NDDG	*National Diabetes Data Group*
NNS	Número necessário para rastrear (*number needed to screen*)
NNT	Número necessário para tratar
OMS	Organização Mundial da Saúde
RR	Risco Relativo
SOP	Síndrome dos ovários policísticos
TOTG	Teste oral de tolerância a glicose

RESUMO

INTRODUÇÃO

Diabetes mellitus gestacional (DMG) é um estado de intolerância aos carboidratos, caracterizado por hiperglicemia de intensidade variável detectada durante a gestação. Apesar de ser geralmente assintomático, esse estado hiperglicêmico associa-se a eventos adversos perinatais, como macrossomia e pré-eclampsia, e seu diagnóstico é realizado geralmente através de programas sistemáticos de rastreamento.

Ao longo das últimas cinco décadas, diferentes critérios foram propostos para o diagnóstico do DMG. Atualmente, o critério mais utilizado em nosso meio é o proposto pela Organização Mundial de Saúde (OMS) em 1999. Em 2010, a *International Association of Diabetes and Pregnancy Study Groups* (IADPSG) propôs um novo critério diagnóstico para o DMG, baseado nos resultados do estudo HAPO (*Hyperglycemia and Adverse Pregnancy Outcome).* Nos últimos três anos o critério da IADPSG vem ganhando importância, sendo adotado por diversas organizações, incluindo a *American Diabetes Association* (ADA). O critério proposto pela IADPSG abrange alterações glicêmicas bem mais discretas para a glicemia em jejum e permite o diagnóstico com apenas um valor alterado entre três testados (jejum, 1h e 2hs após sobrecarga glicêmica). Por consequência, classifica como diabetes gestacional um maior número de gestantes do que o critério da OMS de 1999.

Diversas organizações, entre elas a OMS, estão revisando suas recomendações relacionadas ao diagnóstico do DMG. Os artigos desta tese visaram subsidiar decisões do grupo consultivo da OMS para o diagnóstico do diabetes gestacional.

O objetivo geral da tese foi avaliar o impacto da adoção do critério diagnóstico da IADPSG no rastreamento universal do DMG e a qualidade da evidência que apoia essa adoção. Em específico buscou-se: (1) avaliar a efetividade do tratamento do DMG; (2)

estimar o impacto de programas de rastreamento baseados nos critérios diagnósticos da OMS e da IADPSG; (3) estimar a prevalência do DMG de acordo com o critério do IADPSG e o aumento da prevalência com a adoção desse critério.

MÉTODOS

Para os objetivos 1 e 3 foram realizadas revisões sistemáticas da literatura. A primeira revisão sistemática avaliou a efetividade do tratamento específico para o diabetes gestacional, comparado aos cuidados antenatais usuais, em mulheres com DMG diagnosticadas segundo distintos critérios. A segunda revisão sistemática estimou a prevalência global do DMG de acordo com o critério da IADPSG e o seu aumento quando comparado aos demais critérios.

Para o objetivo dois foi realizado um estudo de simulação com o objetivo de avaliar o impacto do rastreamento universal baseado em critérios da OMS e da IADPSG sobre desfechos perinatais. Os parâmetros utilizados foram subsidiados por revisões da literatura.

A avaliação da qualidade da evidência para as questões abrangidas nos três objetivos foi realizada segundo a abordagem proposta pelo *Grading of Recommendations Assessment, Development* and Evaluation (GRADE) *working group.*

RESULTADOS

Há evidência moderada a alta de que o tratamento específico para o DMG, diagnosticado a partir de critérios variados, reduza a incidência dos seguintes eventos adversos materno-fetais: macrossomia fetal (RR=0,47; IC95% 0,34-0,65; NNT=11,4), nascidos grande para a idade gestacional (GIG) (RR=0,57; IC95% 0,47-0,71; NNT=12,2) e pré-eclampsia (*RR=0,61; IC95% 0,46 – 0,81*; NNT=21).

Simulações baseadas no rastreamento universal segundo os critérios da OMS de 1999 e da IADPSG mostram que os dois rastreamentos reduzem a incidência de nascidos GIG em 0,53% (IC 95% 0,37 – 0,74%; NNS = 189) e em 0,85% (IC 95% 0,54 – 1,29%; NNS = 117), e de pré-eclampsia em 0,27% (IC 95% 0,10 – 0,45%; NNS = 376) e em 0,39% (IC 95% 0,15 – 0,65%; NNS = 257), respectivamente. Quando comparado ao critério da OMS, o rastreamento baseado no critério da IADPSG reduz a incidência de nascidos GIG (0,32%; IC 95% 0,09 – 0,63%; NNS = 309) e de pré-eclampsia (0,12%;(IC 95% 0,01 – 0,25%; NNS = 808). Dada a natureza das comparações indiretas realizadas no modelo de simulação, a qualidade da evidência foi considerada muito baixa.

A prevalência global do DMG de acordo com o critério da IADPSG é de 18,7% (IC95% 15,8 – 21,7%; qualidade de evidência baixa), variando de acordo com a região geográfica avaliada. Comparado com o critério da OMS, é esperado um aumento relativo de sua prevalência em 53% (IC95% 23 – 90%; qualidade de evidência baixa)

CONCLUSÕES

O tratamento do DMG reduz eventos adversos relacionados à gestação e a qualidade da evidência é adequada. Contudo, o rastreamento universal do DMG tem um impacto modesto na prevenção de eventos adversos perinatais. O rastreamento segundo o critério diagnóstico proposto pela IADPSG previne maior número de eventos adversos que o critério da OMS de 1999, contudo classifica um maior número de mulheres como portadoras de diabetes gestacional. Portanto, a adoção desse critério tem implicações econômicas e de utilização de serviços de saúde, que precisam ser consideradas e avaliadas em nível local para sua implementação.

ABSTRACT

BACKGROUND

Gestational diabetes mellitus (GDM) is a state of carbohydrate intolerance characterized by hyperglycemia of variable intensity detected during gestation. Although generally asymptomatic, this hyperglycemic state is associated with perinatal adverse events, such as macrosomia and preeclampsia, and its diagnosis is usually performed through systematic screening programs.

Over the last five decades, different criteria have been proposed for the diagnosis of GDM. Currently, the criteria proposed by the World Health Organization (WHO) in 1999 is the most used in Brazil. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed a new diagnostic criteria for GDM, based on the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. In the last three years, the IADPSG criteria has gained importance, being adopted by several organizations, including the American Diabetes Association (ADA). The criteria proposed by the IADPSG has low a cutoff for fasting glycemia and allows the diagnosis with only one abnormal value among three glycemic evaluation (fasting, 1h and 2h after glycemic overload). As a consequence, it classifies more pregnant women as GDM than the 1999 WHO criteria.

Several organizations, including the WHO, are reviewing their recommendations related to the diagnosis of GDM. The articles of this thesis aimed to support decisions of the WHO advisory group for the diagnosis of gestational diabetes.

The objective of this thesis was to evaluate the impact of the adoption of the IADPSG diagnostic criteria in the universal screening of GDM and the quality of the evidence that supports its adoption. Specifically, we aimed to: (1) evaluate the

effectiveness of GDM treatment; (2) estimate the impact of screening programs based on the WHO and IADPSG diagnostic criteria; (3) estimate the prevalence of GDM according to the IADPSG criteria and the GDM prevalence increase with the adoption of this criteria.

METHODS

For the objectives 1 and 3, we conducted systematic reviews of the literature. The first systematic review evaluated the effectiveness of specific treatment for gestational diabetes, compared to usual antenatal care, in women with GDM diagnosed according to different criteria. The second systematic review estimated the overall prevalence of GDM according to the IADPSG criteria and its increase when compared to other criteria for the condition

For the objective 2, a simulation study was conducted to evaluate the impact of universal screening based on 1999 WHO and IADPSG criteria on perinatal outcomes.

The quality of evidence was assessed according to the approach proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

RESULTS

There is moderate to high quality of evidence that treatment for GDM reduces the incidence of the following maternal-fetal adverse events: macrosomia (RR = 0.47, 95% CI 0.34-0.65; NNT = 11.4), large for gestational age (LGA) births (RR = 0.57, 95% CI 0.47-0.71; NNT = 12.2), and preeclampsia (RR = 0.61, 95% CI 0.46-0.81; NNT = 21).

Simulations based on universal screening strategies according to the 1999 WHO criteria and the IADPSG criteria showed that both reduce the incidence of LGA births in

0.53% (95% CI 0.37 to 0.74%; NNS = 189) and 0.85% (95% CI 0.54-1.29%, NNS = 117) and preeclampsia in 0.27% (95% CI 0.10-0.45%, NNS = 376) and in 0.39% (95% CI 0.15-0.65%, NNS = 257), respectively. When compared to the WHO criteria, screening based on the IADPSG criteria reduces the incidence of LGA births (-0.32%, 95% CI -0.09 to -0.63%, NNS = 309) and preeclampsia (-0.12, 95% CI -0.01 to -0.25%, NNS = 808). Given the nature of the indirect comparisons made in the simulation model, the quality of the evidence was considered very low.

The overall prevalence of DMG according to the IADPSG criteria is 18.7% (95% CI: 15.8 - 21.7%, low quality of evidence), varying according to the geographic region evaluated. Compared to the 1999 WHO criteria, the expected relative increase in prevalence is 53% (95% CI 23-90%, low quality of evidence)

CONCLUSION

Treatment of GDM reduces adverse events related to pregnancy and the quality of evidence regarding its effectiveness is adequate. However, universal screening of GDM has only a modest absolute impact on the prevention of perinatal adverse events. Screening according to the diagnostic criteria proposed by the IADPSG reduces the number of adverse events compared to a screening strategy according to the 1999 WHO criteria, but it classifies a larger number of women as having gestational diabetes. Therefore, the adoption of this criteria for GDM screening has a negative impact on cost and resourses use that need to be considered for its implementation.

APRESENTAÇÃO

Este trabalho consiste no projeto da tese de doutorado intitulada “IMPACTO DO RASTREAMENTO DO DIABETES MELLITUS GESTACIONAL SEGUNDO OS CRITÉRIOS DA ASSOCIAÇÃO INTERNACIONAL DE GRUPOS DE ESTUDO EM DIABETES E GRAVIDEZ”, a ser apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul, em 17 de Junho de 2013. O trabalho é apresentado em três partes, na ordem que segue:

1. Introdução, Revisão da Literatura e Objetivos
2. Artigos
3. Conclusões e Considerações Finais.

INTRODUÇÃO

O diabetes gestacional é um estado hiperglicêmico detectado na gestação e que associa-se à ocorrência eventos adversos perinatais (Lowe 2008, Metzger 2008, Ali 2011, Wendland 2011; Wendland 2012). Mesmo graus discretos de hiperglicemia conferem aumento de risco. (Lowe 2008, Metzger 2008, Chen, 2010, Yogev 2010) Contudo, a definição precisa do que constitui diabetes gestacional que requer intervenção para redução de risco vem sendo matéria de importante controvérsia, gerando incertezas na prática clínica e dificultando a área de pesquisa nas últimas décadas. A maior razão para a grande celeuma diagnóstica é a diversidade de critérios diagnósticos utilizados, envolvendo diferenças nos exames e nos pontos de cortes empregados.

Estratégias de rastreamento para o diabetes mellitus gestacional vêm sendo propostas e utilizadas para prevenir eventos adversos perinatais associados à intolerância à glicose na gestação; entretanto as evidências acerca de sua efetividade e da magnitude do seu benefício são escassas. (Tieu 2010, Farrar 2011)

Atualmente o critério diagnóstico mais utilizado em nosso meio é o proposto em 1999 pela Organização Mundial de Saúde (OMS). (Alberti 1998, World Health Organization 1999) Em 2010, o *International Association of Diabetes and Pregnancy Study Group* (IADPSG) propôs um novo critério diagnóstico, mais abrangente, contudo classificando com diabetes gestacional um maior número de gestantes.(Metzger 2010) Não há estudos que comparam o uso desses dois critérios diagnósticos em estratégias de rastreamento.

A presente tese visou avaliar o impacto do rastreamento universal do DMG baseado nos critérios diagnósticos da IADPSG e da OMS de 1999 e classificar a qualidade da evidência que apoia sua utilização.

Os artigos da tese resultaram de um trabalho que visou subsidiar decisões do grupo consultivo da Organização Mundial da Saúde para a detecção do diabetes gestacional (WHO Consultation on the Diagnosis and Screening of Gestational Diabetes Mellitus), tendo sido realizado via contrato com a Dra. Maria Inês Schmidt, co-orientadora desta tese de doutorado.

3. REVISÃO DE LITERATURA – DIABETES MELLITUS GESTACIONAL

3.1. DEFINIÇÃO

Diabetes mellitus gestacional (DMG) é intolerância aos carboidratos, de intensidade variável, e com diagnóstico durante a gestação (Metzger 1998, Metzger 2010)

O diagnóstico de DMG não exclui a possibilidade de a intolerância glicêmica ter iniciado antes da gravidez e ter se mantido sem diagnóstico até a gestação em curso. O *National Collaborating Centre for Women's and Children's Health* (Reino Unido) estima que aproximadamente 87,5% das gestações com diabetes são classificadas como diabetes gestacional; 7,5% como diabetes tipo 1 e os demais 5%, como diabetes tipo 2.(National Collaborating Centre for Women's and Children's Health 2008) Resultados semelhantes foram observados em nosso meio; em estudo realizado no Hospital de Clínicas de Porto Alegre, de 173 gestantes atendidas no ambulatório de gestação e diabetes, o diabetes gestacional ocorreu em 84% das gestantes, 8% apresentaram diabetes tipo 2, 6%, diabetes tipo 1 e 2%, outros tipos. (Weinert 2011)

3.2. FISIOPATOLOGIA

Todas as gestantes desenvolvem, em algum grau, resistência insulínica. Essa adaptação é necessária para fornecer as necessidades de desenvolvimento e crescimento do feto, bem como, para preparar o organismo materno para o parto e lactação. (Barbour 2007, Lain 2007) Este processo fisiológico ocorre provavelmente em resposta a produtos

placentários, como fator de necrose tumoral alfa e hormônio de crescimento humano placentário.

A resistência insulínica pode progredir para DMG devido a distúrbios funcionais (genéticos ou autoimunes) das células beta-pancreáticas e / ou devido à piora da resistência insulínica crônica. (Evensen 2012) A resistência insulínica é mais acentuada no terceiro trimestre gestacional, e assim como no diabetes mellitus tipo 2, sua origem é considerada multifatorial e poligenética, com diferentes variantes genéticas interagindo com fatores ambientais para desencadear a doença.

3.3. EPIDEMIOLOGIA

A prevalência do DMG varia entre - em média - de 1 a 14%, dependendo da região geográfica, das características étnicas e sociais da população e do critério diagnóstico utilizado.(Hunt 2007) A prevalência do DMG aumentou marcadamente nos últimos anos, em parte devido à epidemia de obesidade (Ferrara 2004). Além disso, com a revisão de atuais critérios diagnósticos, que tendem a classificar um maior número de gestantes como doentes, a prevalência tenderá a aumentar de forma expressiva. (Metzger 2010, Langer 2013) Alguns artigos recentes relatam taxas de prevalência superior a 30% em determinadas regiões, como no Oriente Médio.(Agarwal 2010, Agarwal 2012) No Brasil, em torno de 7 a 8% das gestações são complicadas pelo diabetes gestacional quando definido de acordo com o critério diagnóstico de 1999 da Organização Mundial da Saúde (OMS).(Schmidt 2001) O terceiro artigo da presente tese abordará aspectos relacionados à prevalência do diabetes gestacional segundo o novo critério.

3.4. FATORES DE RISCO PARA O DIABETES GESTACIONAL

Vários fatores de risco para o DMG têm sido identificados de forma consistente enquanto que outros ainda permanecem controversos. Muitos desses fatores de risco são os mesmos que predizem diabetes mellitus fora da gravidez. Entre os fatores de risco para DMG destacam-se:

- Idade materna avançada: a diminuição da reserva funcional das células beta-pancreáticas é correlacionada à idade. (Solomon 1997)
- Sobrepeso e obesidade: associadas à resistência insulínica, o que é agravado pela gravidez. As chances de desenvolvimento de DMG em mulheres com sobrepeso e obesidade são 97% e 201% maiores do que as chances em gestantes eutróficas no período pré-gravídico. (Solomon 1997. Torloni 2009)
- História familiar de diabetes mellitus tipo 2, devido à provável etiologia poligenética do DMG.(Solomon 1997)
- Sedentarismo: atividade física favorece a perda de peso e diminui a resistência insulínica; a atividade física no período pré-gestacional e no início da gravidez estão associadas a um risco 55% e de 24% menor de desenvolver DMG, respectivamente (Tobias 2011)
- Síndrome dos ovários policísticos (SOP): associado à resistência insulínica e obesidade. As chances de desenvolvimento de DMG em mulheres com SOP são 189% maiores do que indivíduos sem a doença. (Toulis 2009)
- Dieta pobre em fibras e com alto índice glicêmico. (Zhang 2006)
- DMG em gestação prévia: a recorrência de DMG varia entre 30 e 84%, dependendo da população estudada. (Kim 2007)

O tabagismo, apesar de estar associado a um aumento de 40 a 50% na incidência de diabetes mellitus tipo 2,(Willi 2007) não está definido como fator de risco no DMG, uma vez que estudos vêm apresentando resultados inconsistentes. (Wendland 2008) Os fatores de risco para o DMG são apresentados no quadro 1.

Quadro 1 – Fatores de risco para o diabetes mellitus gestacional. Adaptado de Reichelt 2002

- Idade superior a 25 anos;
- Obesidade ou ganho excessivo de peso na gravidez atual;
- Deposição central excessiva de gordura corporal;
- História familiar de diabetes em parentes de 1º grau;
- Baixa estatura (<1,50cm);
- Crescimento fetal excessivo, polidrâmnio, hipertensão ou pré-eclâmpsia na gravidez atual;
- Antecedentes obstétricos de morte fetal ou neonatal, de macrossomia ou de diabetes gestacional.

3.5. ASSOCIAÇÃO ENTRE HIPERGLICEMIA MATERNA E EVENTOS ADVERSOS PERINATAIS

Ao longo de cinco décadas, diversos estudos observacionais bem delineados avaliaram diretamente a associação entre níveis glicêmicos – avaliado através de diferentes critérios diagnósticos – e eventos adversos perinatais materno-fetais. Mais de 50.000 gestações foram avaliadas, sendo observada associação positiva e consistente entre diferentes estudos e populações.(Wendland 2012) Apesar da presença de confundimento residual não poder ser descartado, ajustamento foi realizado para os principais confundidores (raça, idade materna, paridade, índice de massa corpora e ganho

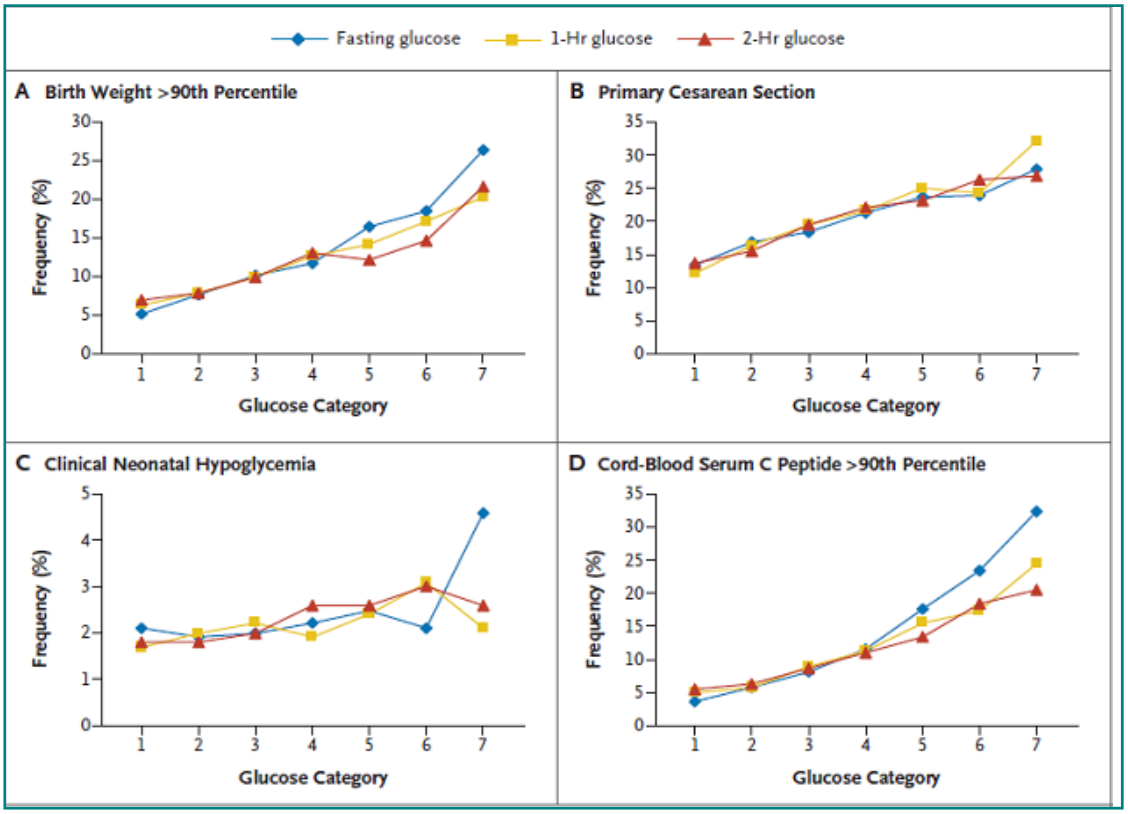
de peso gestacional), com as associações se mantendo clinicamente importante e estatisticamente significativas em vários estudos.(Pettitt 1980, Sermer 1995, Schmidt 2001, Metzger 2008, Black 2010, Sacks, 2010, O'Sullivan 2011)

O estudo mais abrangente é o estudo HAPO (*Hyperglycemia and adverse pregnancy outcomes*), um estudo de coorte multicêntrico, envolvendo vários países da América do Norte, Caribe, Europa, Ásia, Austrália e Oriente Médio, incluindo 25.505 gestantes.(Contreras 2002, Metzger 2008) O estudo HAPO foi desenvolvido para responder questões sobre a associação entre a glicemia materna (em graus de hiperglicemia menores que o diabetes mellitus) e desfechos adversos na gravidez, sendo realizado com forte rigor metodológico, apresentando pequeno risco de vieses. A hiperglicemia materna associou-se com maior incidência de nascidos grandes para a idade gestacional, distócia de ombro, pré-eclampsia, parto cesáreo, nascimentos pré-termos e níveis mais elevados de peptídeo C no cordão umbilical. A incidência dos eventos correlacionou-se com o nível de glicemia materna, como pode ser observado na figura 1.

Recentemente, reanálise do Estudo Brasileiro de Diabetes Gestacional (EBDG) encontrou associação estatisticamente significativa entre hiperglicemia materna e mortalidade fetal.(Wendland 2011) A associação entre o DMG e malformações congênitas também está descrita.(Balsells 2012)

Em resumo, a literatura é consistente, apontando para importante relação causal entre hiperglicemia e eventos adversos perinatais.

Figura 1: Frequências de desfechos primários nas categorias de glicemia do estudo HAPO. Adaptado de Metzger 2008.



Categorias de glicemias (mg/dl) de jejum: 1) < 75; 2) 75 – 79; 3) 80 – 84; 4) 85 – 89; 5) 90 – 94; 6) 95 – 99; 7) ≥ 100; de 1-h após sobrecarga com 75g: 1) ≤ 105; 2) 106 – 132; 3) 133 – 155; 4) 156 – 171; 5) 172 – 193; 6) 194 – 211; 7) ≥ 212; de 2-h após sobrecarga com 75g: 1) < 90; 2) 91 – 108; 3) 109 – 125; 4) 126 – 139 ; 5) 140 – 157; 6) 158 – 177; 7) ≥ 178.
Dados ajustados, entre outras variáveis, por centro de estudo, idade materna, idade gestacional, índice de massa corporal e história familiar de diabetes.

3.6. DIAGNÓSTICO

As mulheres com DMG são consideradas gestações de alto risco para complicações perinatais, assim, geralmente sendo referenciadas a serviços especializados para realizar seu acompanhamento pré-natal, o que acarreta custos e utilização de recursos dos sistemas.

Uma vez que a associação entre valores glicêmicos e eventos adversos perinatais segue um padrão contínuo, foram propostos diversos pontos de corte para os níveis glicêmicos ao longo do tempo. O primeiro critério proposto para o diagnóstico de DMG foi o de O´Sullivan e Mahan em 1964, com sobrecarga de 100g de glicose, definindo como DMG a presença de dois ou mais valores glicêmicos alterados (jejum ≥90mg/dL, 1h ≥165mg/dL, 2hs ≥145mg/dL e 3hs ≥125mg/dL).(O'Sullivan 1964)

O diagnóstico no Brasil é geralmente realizado em duas etapas. Primeiramente é solicitada uma glicemia em jejum e após, para as classificadas como rastreamento positivo, é recomendado um teste de sobrecarga oral de glicose (75 ou 100g), após jejum de 8 a 14 horas. No Brasil, o critério diagnóstico mais utilizado deriva-se do proposto pela Organização Mundial de Saúde (OMS) em 1999,(Albert 1998, World Health Organization 1999) frequentemente abrangendo também um ponto de corte inferior ao de diabetes para a glicemia em jejum (≥110mg/dL).(Reichelt 2002) A OMS atualmente está revendo suas recomendações relacionadas ao diagnóstico do DMG sendo esperado um posicionamento oficial da entidade ainda em 2013.

Em 2010, a *International Association of Diabetes and Pregnancy Study Groups* (IADPSG) propôs um novo critério diagnóstico para o DMG.(Metzger 2010) A escolha dos pontos de corte de glicemia foi baseada nos dados do estudo HAPO. Para tanto, foram considerados os desfechos peso ao nascer, peptídeo C do cordão umbilical e porcentagem de gordura corporal do bebê. Para derivar os pontos de corte para o critério diagnóstico, foram tomadas as médias dos valores de glicemia que alcançavam uma razão de chances da ordem de 1,75. Nos últimos três anos o critério da IADPSG vem ganhando aceitação, sendo adotado por diversas organizações, incluindo a *American Diabetes Association* (ADA).(American Diabetes Association 2012)

Na tabela 1 são apresentados os critérios diagnósticos mais utilizados atualmente. (National Diabetes Data Group 1979, Carpenter 1982, Alberti 1998, World Health Organization 1999, American Diabetes Association 2010, Meztger 2010, American Diabetes Association 2012)

Tabela 1 – Principais critérios diagnósticos para o diabetes mellitus gestacional

Critério diagnóstico	Sobrecarga glicose	Pontos de corte glicêmicos (mg/dL)				Valores alterados para o diagnóstico
		Jejum	1h	2h	3h	
NDDG	100g	≥ 105	≥ 190	≥ 165	≥ 145	≥ 2
Carpenter & Coustan	100g	≥ 95	≥ 180	≥ 155	≥ 140	≥ 2
ADIPS	75g	≥ 99	-	≥ 144	-	≥ 1
OMS (1999)[1]	75g	≥ 126	-	≥ 140	-	≥ 1
ADA (até 2010)	75g	≥ 95	≥ 180	≥ 155	-	≥ 1
IADPSG / ADA	75g	≥ 92	≥ 180	≥ 153	-	≥ 1

[1] O critério diagnóstico da OMS atualmente encontra-se em revisão
NDDG: *National Diabetes Data Group;* ADIPS: *Australian Diabetes in Pregnancy Society;* OMS: Organização Mundial de Saúde; ADA: *American Diabetes Association.* IADPSG: *International Association of Diabetes and Pregnancy Study Group*;

3.7. PROPRIEDADES PROGNÓSTICAS DOS CRITÉRIOS PARA O DIABETES GESTACIONAL

Os critérios diagnósticos para o DMG são baseados em suas propriedades prognósticas, visando classificar gestantes em maior risco para desenvolver eventos adversos perinatais. Wendland et al avaliaram a capacidade prognóstica dos critérios da OMS e do IADPSG em predizer eventos clínicos.(Wendland, Torloni, 2012) Em geral, ambos os critérios identificam mulheres em risco 25 a 75% maior de apresentarem eventos adversos perinatais. (tabela 2)

Tabela 2 – Aumento no risco de eventos adversos materno-fetais de acordo com diferentes critérios diagnósticos para diabetes mellitus gestacional. Adaptado de Wendland et al., 2012. (Wendland, Torloni, 2012)

	Gestantes com DMG de acordo com o critério da OMS (1999)	Gestantes com DMG de acordo com o critério do IADPSG (2010)
Nascidos GIG	51% (IC 95%: 39% a 69%)	73% (IC 95%: 28% a 135%)
Pré-eclampsia	69% (IC 95%: 31% a 118%)	71% (IC 95%: 38% a 113%)
Parto cesáreo	37% (IC 95%: 24% a 51%)	23% (IC 95%: 1% a 51%)

DMG: diabetes mellitus gestacional; OMS: Organização Mundial de Saúde; IADPSG: *International Association of Diabetes and Pregnancy Study Group*; GIG: grande para a idade gestacional; IC: intervalo de confiança

3.8. TRATAMENTO

O tratamento do DMG consiste em cuidados pré-natais intensivos, dieta, atividade física, monitorização glicêmica e uso de anti-diabéticos quando necessário, em geral de insulina. O tratamento é efetivo em reduzir eventos perinatais como macrossomia, pré-eclampsia e distócia de ombro.(Falavigna 2013) O primeiro artigo da presente tese abordará medidas sumárias de efetividade do tratamento do DMG.

3.9. RASTREAMENTO

O DMG é geralmente assintomático, sendo diagnosticado principalmente através de rastreamento sistemático após a 24ª semana de gestação. Evidências avaliando o rastreamento são escassas;(Tieu 2010) contudo o rastreamento é recomendado com base na associação entre hiperglicemia com eventos adversos perinatais, e da efetividade do

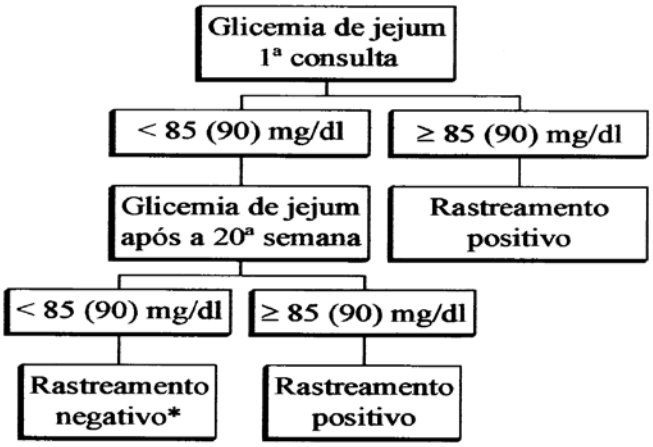
tratamento para a prevenção desses eventos. Há poucos subsídios na literatura que permitam orientar a escolha entre as diferentes estratégias de rastreamento existentes.(Farrar 2011)

Apesar de haver consenso entre os especialistas sobre a necessidade de realizar o rastreamento para o DMG, a forma a ser realizada, assim como o critério diagnóstico a ser utilizado, são motivos de grande discussão. Alguns preconizam o rastreamento universal e outros, o rastreamento seletivo, em gestantes com fatores de risco para otimização de recursos. Além disso, é comum a realização da estratégia de rastreamento em dois estágios; nesses casos, geralmente o TOTG é realizado apenas em gestantes com valores elevados na glicemia de jejum ou no teste de sobrecarga glicêmica (dosagem de glicemia 1h após a ingestão de 50g de glicose, não sendo necessário jejum).

No Brasil é preconizada estratégia de rastreamento em dois estágios. De acordo com essas recomendações, a glicemia em jejum é realizada na primeira consulta pré-natal e na 20ª semana gestacional (figura 2). Caso os valores da glicemia em jejum encontrem-se elevados, procede-se com a realização do TOTG (figura 3).

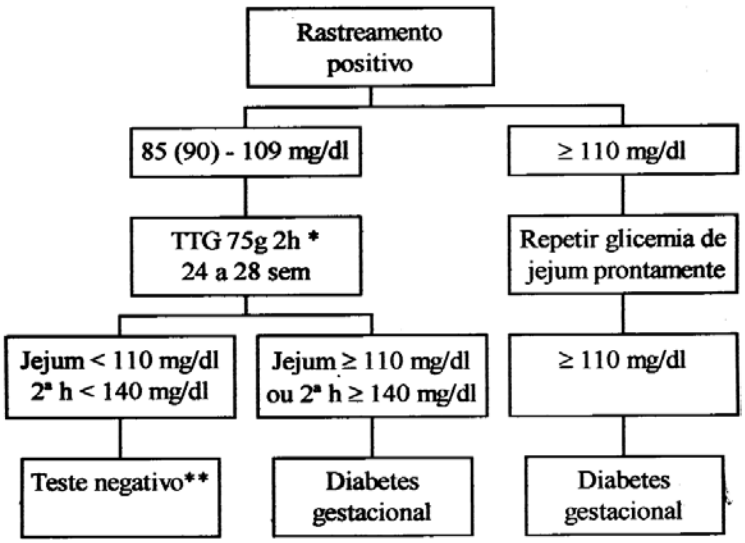
O segundo artigo da presente tese abordará o o rastreamento universal utilizando os critérios diagnósticos da OMS de 1999 e da IADPSG.

Figura 2. Estratégia de rastreamento para diabetes gestacional. Adaptado de Reichelt 2002



*Gestantes devem repetir a GPJ após a vigésima semana de gestação.

Figura 3. Estratégia de diagnóstico para Diabetes gestacional Adaptado de Reichelt 2002



*Alternativa com carga de 100 g e pontos de corte de critério previamente utilizado pela ADA vigente até 2010).
**No caso de forte suspeita pode-se repetir glicemia de jejum ou TOTG

4. OBJETIVOS

JUSTIFICATIVA

- Frente às controvérsias a respeito do diagnóstico do DMG e com a adoção crescente do recente critério diagnósticos da *International Association of Diabetes and Pregnancy Study Groups* (IADPSG), são necessários estudos que avaliem seu impacto e o compare com o de outros critérios existentes para subsidiar sua implementação. Os artigos desta tese visaram subsidiar decisões do grupo consultivo da Organização Mundial da Saúde para o diagnóstico do diabetes gestacional.

OBJETIVO GERAL

Avaliar o impacto do rastreamento universal do diabetes mellitus gestacional baseado nos critérios diagnósticos da IADPSG e a qualidade da evidência que apoia sua adoção.

OBJETIVOS ESPECÍFICOS

1. Avaliar a efetividade do tratamento para o diabetes mellitus gestacional, comparado aos cuidados antenatais usuais, na prevenção de desfechos adversos da gravidez.
2. Por meio de estudo de simulação, avaliar o impacto do rastreamento universal para o diabetes mellitus gestacional segundo o critério

diagnóstico proposto pela IADPSG, quando comparado ao impacto obtido com o critério da Organização Mundial de Saúde de 1999; e classificar a qualidade da evidência que apoia a adoção dos dois critérios.

3. Estimar a prevalência do diabetes mellitus gestacional de acordo com o critério proposto pela IADPSG e o aumento de sua prevalência em relação aos demais critérios diagnósticos.

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6. ARTIGO 1 – EFETIVIDADE DO TRATAMENTO DO DIABETES GESTACIONAL

Effectiveness of Gestational Diabetes Treatment: a Systematic Review with Quality of Evidence Assessment

[Efetividade do Tratamento do Diabetes Mellitus Gestacional: Revisão Sistemática, com Avaliação da Qualidade da Evidência]

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SUMÁRIO - FETIVIDADE DO TRATAMENTO DO DIABETES MELLITUS GESTACIONAL: REVISÃO SISTEMÁTICA COM AVALIAÇÃO DA QUALIDADE DA EVIDÊNCIA

INTRODUÇÃO

Diabetes mellitus gestacional (DMG) é intolerância aos carboidratos, de intensidade variável, e com diagnóstico durante a gestação. O tratamento do DMG consiste em cuidados pré-natais intensivos, dieta, atividade física, monitorização glicêmica e uso de anti-diabéticos quando necessário; tem como objetivo reduzir a incidência de eventos adversos relacionados à hiperglicemia.

O objetivo do presente estudo é avaliar a efetividade do tratamento específico do DMG, comparado aos cuidados pré-natais usuais, em gestantes com diagnóstico de DMG. Adicionalmente, avaliar a qualidade da evidência de acordo com o *Grading of Recommendations Assessment, Development and Evaluation* (GRADE).

MÉTODOS

Delineamento: Revisão sistemática de estudos de intervenção, com meta-análise.

Estratégia de busca: Quatorze diferentes bases eletrônicas (African index medicus; CENTRAL; ClinicalTrials.gov register; EMBASE; IMEMR; IMSEAR; IndMED; ISI Web of Knowledge; KoreaMed; LILACS; Panteleimon; PubMed; WHO.int trial search; and WPRIM**),** sendo realizada em fevereiro de 2012; adicionalmente foram avaliadas lista de referências de artigos relevantes

Seleção dos estudos: realizada independentemente por dois investigadores; incluídos estudos de intervenção que comparam o tratamento específico para o DMG a cuidados antenatais usuais. Estudos quasi-randomizados foram incluídos caso utilizassem método

de alocação sistemática (por exemplo, alternância).

Extração de dados: realizada independentemente por dois investigadores utilizando formulário padronizado para coleta de dados.

Análise de dados: dados agregados em meta-análise de efeitos aleatórios. Dados apresentados em risco relativo(RR) e número necessário para tratar(NNT), com intervalos de confiança(IC) de 95%. Análises realizadas com o software *R* versão 2.1.11, pacote *Metafor 1.6-0.*

Avaliação da qualidade metodológica: avaliação da qualidade dos estudos individuais realizada de acordo com o *Cochrane Handbook for Systematic Reviews of Interventions***.** Avaliação da qualidade da evidência (QdE) para o conjunto da evidência realizada de acordo com a abordagem GRADE.

RESULTADOS

Inclusão dos estudos: Foram revisados 3817 resumos, sendo selecionados 42 artigos para avaliar sua elegibilidade. Foram incluídos na revisão sistemática 8 publicações, referentes a 7 estudos, avaliando 3157 gestações. Os estudos foram conduzidos na Austrália, no Canadá, em Hong Kong, no Reino Unido e nos Estados Unidos. O espectro da hiperglicemia e os critérios diagnósticos utilizados variaram entre os estudos; as intervenções consistiam em geral em dieta, mudanças no estilo de vida e, quando necessário, insulina. Dos sete estudos incluídos, quatro eram randomizados enquanto os outros três estudos possuíam alocação baseada em alternância. Nenhum dos estudos era duplo-cego e em apenas um estudo as perdas de seguimento não foram adequadamente descritas.

Desfechos perinatais: o tratamento específico para o diabetes gestacional reduziu a incidência de macrossomia (RR=0,47; IC95% 0,34-0,65; NNT=11,4; QdE alta), de

nascidos grande para a idade gestacional (RR=0,57; IC95% 0,47-0,71; NNT=12,2; QdE alta) e distócia de ombro (RR=0,41; IC95% 0,22-0,76; NNT=48,8; QdE baixa). Não foi observado efeito estatisticamente significativo para mortalidade perinatal (RR=0,62; IC95% 0,31-1,24; QdE muito baixa); internação em unidade de cuidado intensivo neonatal (RR=0,75; IC95% 0,52 – 1,08; QdE baixa); trauma fetal (RR=0,39; IC95% 0,11 – 1,35; QdE baixa); nascidos pequenos para a idade gestacional (RR=1,05; IC95% 0,77 – 1,44; QdE moderada); nascimentos pré-termo (RR=0,90; IC95% 0,67 – 1,21; QdE baixa); anormalidades congênitas (RR=0,81; IC95% 0,55 – 1,18; QdE muito baixa); hiperbilirrubinemia (RR=0,81; IC95% 0,63 – 1,04; QdE baixa); hipoglicemia neonatal (RR=1,16; IC95% 0,90 – 1,49; QdE muito baixa) e síndrome da angustia respiratória (RR=1,05; IC95% 0,48 – 2,28; QdE muito baixa).

Desfechos maternos: não houve mortes maternas nos estudos incluídos na revisão. O tratamento específico para o diabetes gestacional reduziu a incidência de pré-eclampsia (RR=0,61; IC95% 0,46 – 0,81; NNT=21; QdE moderada) e de distúrbios hipertensivos na gestação, que inclui hipertensão diagnosticada na gestação e pré-eclampsia (RR=0,64; IC95% 0,51 – 0,81; NNT=18,1; QdE moderada). Não foi observado efeito estatisticamente significativo para parto cesário (RR=0,90; IC95% 0,78-1,05; QdE moderada) e futuro desenvolvimento de diabetes mellitus tipo 2 na mãe (RR=0,98; IC95% 0,79 – 1,21; QdE baixa).

CONCLUSÕES

O tratamento para o DMG é efetivo em reduzir eventos adversos importantes relacionados à gestação. A redução absoluta de eventos é clinicamente importante para desfechos como pré-eclampsia e macrossomia, e a qualidade da evidência é moderada e alta para esses desfechos. Adicionalmente, não foi observado aumento de potenciais

eventos adversos do tratamento como, por exemplo, hipoglicemia neonatal e nascidos pequenos para a idade gestacional.

Effectiveness of Gestational Diabetes Treatment: a Systematic Review with Quality of Evidence Assessment

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ABSTRACT

AIMS: To evaluate the effectiveness of gestational diabetes (GDM) treatment compared to usual antenatal care, in the prevention of adverse pregnancy outcomes. Additionally, to assess the quality of the evidence to support GDM treatment according to GRADE guidelines.

METHODS: Fourteen electronic databases and reference lists of relevant literature were searched for articles published from inception to February, 2012. Controlled clinical trials comparing GDM treatment to usual antenatal care were included. Independent extraction of articles was done by two authors using predefined data fields.

RESULTS: Seven trials involving 3157 women were included. We found high quality evidence that treatment of GDM reduces macrosomia (RR=0.47; 95% CI, 0.34-0.65; NNT=11.4) and large for gestational age birth (RR=0.57; 95% CI, 0.47-0.71; NNT=12.2); moderate quality evidence that treatment reduces preeclampsia (RR=0.61; 95% CI, 0.46-0.81; NNT=21.0) and hypertensive disorders in pregnancy (RR=0.64; 95% CI, 0.51-0.81; NNT=18.1); and low quality evidence that treatment reduces shoulder dystocia (RR=0.41; 95% CI, 0.22-0.76; NNT=48.8). No statistically significant reduction was seen for caesarean section. No increase in small for gestational age or preterm birth was found.

CONCLUSIONS: Treatment of GDM is effective in reducing macrosomia (high quality evidence), preeclampsia and shoulder dystocia.

INTRODUCTION

Gestational diabetes mellitus (GDM) has been defined as glucose intolerance of variable severity with onset or first recognition during pregnancy.[1] The incidence of GDM has increased markedly in recent years in large part due to the obesity epidemic[2] and will increase further with the adoption of the diagnostic criteria proposed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG),[3] recently adopted by the American Diabetes Association.[4]

GDM is generally asymptomatic, usually being detected through systematic screening after the 24th week of pregnancy. Evidence to support screening for GDM is indirect and strongly based on the potential adverse effects of hyperglycemia on pregnancy outcomes,[5–8] and on the effectiveness of GDM treatment in preventing these outcomes.[9,10] Two systematic reviews have summarized the evidence available for the effectiveness of GDM treatment.[11,12] The first, performed by Alwan et al., was conducted prior to the publication of the Landon et al. study, a large and well-designed randomized trial.[10] The second, conducted by Horvath et al, did not evaluate preeclampsia, a common and clinically important complication of pregnancy, found to be reduced by in recent GDM trials.[9,10]

The WHO will soon issue a report on the diagnosis of GDM. To contribute to the evidence-based recommendations of this report, we performed a comprehensive and updated systematic review for the effectiveness of GDM treatment, when compared to usual antenatal care, in the prevention of adverse pregnancy outcomes, including preeclampsia. Additionally, given the importance of documented treatment benefit in the decision to recommend screening, we assessed the quality of the evidence for GDM treatment according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.[13]

METHODS

We performed this review according to Cochrane Handbook for Systematic Reviews of Intervention[14] and report data following PRISMA statement recommendations.[15] Level of evidence was assessed for each outcome according to GRADE.[13] This review is part of the support material prepared for the WHO Consultation on the Diagnosis and Screening of Gestational Diabetes Mellitus held in Geneva on November 29 to December 1, 2010.

Eligibility Criteria

We included controlled clinical trials comparing GDM treatment to usual antenatal care for pregnant women with a diagnosis of GDM according to the individual study definitions. No restrictions were made regarding language, or publication date or status.

In accordance with the Cochrane Handbook for Systematic Reviews of Interventions,[14] we included studies with random allocation or systematic quasi-random allocation, such as alternation. We excluded experimental studies using non-systematic treatment allocation methods such as clinician judgment, subject preference or availability of the intervention.

Outcomes of interest

Outcomes were extracted according to the study author´s definitions, which varied for most outcomes.

Perinatal outcomes were perinatal mortality, macrosomia, large for gestational age (LGA) and small for gestational age (SGA) birth, neonatal intensive care unit (ICU) admission, congenital abnormalities, preterm birth, birth trauma (defined as bone fracture

or brachial plexus palsy), shoulder dystocia, neonatal hypoglycemia, hyperbilirubinemia and respiratory distress syndrome.

Maternal outcomes were maternal mortality, preeclampsia and hypertensive disorders in pregnancy, caesarean section and diabetes later in life.

Literature Search and Study Selection

The search strategy used the following general terms, adapted to each database: “gestational diabetes”, “random*”, “controlled clinical trial”, “diabet*” and “pregnan*”. Terms used for the electronic search are detailed in Supplementary Table 1.

We searched 14 electronic databases (African index medicus; CENTRAL; ClinicalTrials.gov register; EMBASE; IMEMR; IMSEAR; IndMED; ISI Web of Knowledge; KoreaMed; LILACS; Panteleimon; PubMed; WHO.int trial search; and WPRIM) for articles published from inception up to February 2012.

We also searched for additional studies by reviewing the reference lists of review articles and of controlled clinical trials, including the list of excluded studies from other systematic reviews.

All citations identified were entered into an electronic database, and duplicates were deleted. Initially, two investigators independently screened potentially relevant studies through the titles and abstracts. When the information was not sufficient to determine if the article was eligible for inclusion, a full text was obtained for further evaluation. Discrepancies were discussed until consensus was reached.

Data Management

Two independent investigators reviewed the eligible studies and extracted data using a standardized form. Information extracted from each individual trial consisted of: (1)

characteristics of trial participants (population source, age, ethnicity and pre-gravid BMI); (2) diagnostic procedures (type of test used, gestational age at testing, GDM diagnostic criteria and results for oral glucose tolerance and glucose challenge tests); (3) type of intervention (treatment performed and number of women requiring use of anti-diabetics); (4) outcome measures and their definition according to individual studies; and (5) methodological quality of data, as explained below.

Disagreements were discussed until consensus was reached. When quantitative data were not reported, approximate values were obtained from the figures or calculated from proportions.

Assessment of methodological quality: risk of bias

The domains of sequence generation, allocation concealment, blinding (of participants, personnel and outcome assessors), and incomplete outcome data were considered in the evaluation of potential bias in individual studies. Risk of bias was classified as high, uncertain or low, according to the definitions of the Cochrane Handbook.[14]

Data analysis

Data were combined using random-effect meta-analysis models, with restricted maximum-likelihood (REML) variance estimator and presented as relative risks (RR) with 95% confidence intervals (CI). Most statistical analyses were performed using the R version 2.11.1 software, package metafor version 1.6-0.[16] For trial sequential analysis, TSA software was used.[17] To evaluate the impact of treatment, we estimated the number needed to treat (NNT).

We assessed heterogeneity using a standard $\chi 2$ test with a significance level of 0.10. In view of the low power of such tests, we also examined heterogeneity with the I^2

statistic, where I^2 greater than 50% was considered an indicator of high inconsistency across studies.[18]

Since we included trials with quasi-random allocation methods, sensitivity analysis was performed stratifying studies according to allocation concealment quality for all available outcomes.

In addition to REML, we also aggregated data with other variance estimators (maximum likelihood, empirical Bayes, Sidik-Jonkman, and DerSimonean and Laird) and with a fixed effect model, in order to assess model robustness.[19]

Trial sequential analysis was performed for macrosomia, LGA birth, hypertensive disorders in pregnancy and caesarean section in order to determine the sufficiency of the available data.[20] The observed rates in the control groups were used to estimate the incidence of outcomes, as well as their consistency across studies. In these analyses, statistical power was defined as 80% for an alpha of 5%, assuming relative risk reduction (RRR) of 35% for macrosomia, 35% for LGA birth, 25% for hypertensive disorders in pregnancy, and 20% for caesarean section. Publication bias was evaluated using funnel plots and Egger's test based on weighted regression for outcomes with at least five studies.[21] Adjustment for publication bias with the trim and fill method was performed as needed.[22]

RESULTS

After excluding duplicates, our search identified 3817 references. We reviewed all titles and abstracts, identifying 42 potentially relevant studies to be assessed by full text. A total of 8 publications pertaining to 7 studies met the selection criteria and were included in this systematic review, totaling 3157 women randomized.[9,10,23–28] (Supplementary Figure 1) The list of excluded studies (and reasons for exclusions) is available in

Supplementary Table 2. The main characteristics of included studies are presented in Table 1. Studies were conducted in Australia, Canada, Hong Kong, United Kingdom and United States. The spectrum of hyperglycemia among women randomized varied across studies, and the interventions offered generally consisted of a stepped approach of diet and lifestyle changes and, if necessary, insulin.

Methodological quality

Out of the seven studies, random allocation of treatment was performed in four,[9,10,23,24] with systematic quasi-random allocation approaches being employed in the remaining three.[25,26,28] Allocation concealment methods were reported in details in only two trials.[9,10] None of the trials were double-blinded. One trial had incomplete outcome data, and did not describe in which group withdrawals occurred and why.[25] Assessment of the methodological quality of studies included is summarized in Supplementary Table 3.

Perinatal outcomes (Figure 1, Supplementary Figure 2)

LGA birth was defined as birth weight above 90th percentile for gestational age and SGA birth was defined as birth weight below 10th percentile for gestational age in all studies. Macrosomia was defined as a birth weight ≥ 4,000g in all studies except in that of Sullivan et al,[26] in which it was defined as a birth weight ≥ 4,100g. Preterm birth was defined in two studies as a birth before 37 weeks of gestation[10, 24] and in one study as a birth weight ≤ 2,440g.[26]

Infants of women treated for GDM were at significantly lower risk for LGA birth (RR=0.57; 95% CI, 0.47-0.71), macrosomia (RR= 0.47; 95% CI, 0.34-0.65), and shoulder dystocia (RR=0.41; 95% CI, 0.22-0.76) than those receiving usual antenatal care.

Additionally, risk reductions greater than 20%, though not statistically significant, were seen for perinatal mortality, birth trauma and neonatal intensive care admission. In the seven included trials, only three reported a total of 46 perinatal deaths, mostly in the two older, quasi-randomized studies.[26,28] Treatment of GDM did not increase the risk for the two potential adverse effects investigated, preterm birth (RR, 0.90; 95% CI, 0.67-1.21) and small for gestational age birth (RR=1.05; 95% CI, 0.77-1.44). Treatment for GDM did not modify the risks of congenital abnormalities, hyperbilirubinemia, neonatal hypoglycemia and respiratory distress syndrome (Supplementary Figure 2).

The consistency across studies was generally high, except for macrosomia (I^2=48%) and respiratory distress syndrome (I^2=58%). The exclusion of the study done by Garner et al.[23] eliminated the heterogeneity for macrosomia (I^2=0) without major change in the magnitude of the effect (RR=0.41; 95% CI, 0.33-0.52).

Maternal outcomes (Figure 2, Supplementary Figure 3)

No occurrences of maternal deaths were reported in the included trials. High consistency was seen across studies for the effect on maternal outcomes.

Hypertensive disorders in pregnancy included preeclampsia in the ACHOIS trial[9], the presence of hypertension first diagnosed in pregnancy in the Landon et al trial[10] and the presence of pregnancy-induced hypertension or chronic hypertension in the Langer et al study[24].

Treatment of GDM produced a significant reduction in the risk of preeclampsia (RR=0.61; 95% CI, 0.46-0.81) as well as in the larger grouping of hypertensive disorders in pregnancy (RR=0.64; 95% CI, 0.51-0.81). No significant risk reduction was observed for caesarean section (RR=0.90; 95% CI, 0.78-1.05) and for diabetes mellitus later in life (RR=0.98; 95% CI, 0.79-1.21).

Additional analyses

In sensitivity analyses, the exclusion of the three quasi-randomized studies produced minimal changes in the pooled RRs for perinatal mortality, macrosomia, LGA birth and cesarean section (Supplementary Figure 4). Similar analyses performed with different variance estimators had little impact on the effect measured, except for neonatal hypoglycemia (Supplementary Table 4).

Trial sequential analyses for macrosomia, LGA birth, hypertensive disorders in pregnancy and caesarean section revealed sufficient data for making inference for these outcomes (Supplementary Figure 5).

Publication bias was evaluated for macrosomia and cesarean section. There was a small, non-significant asymmetry in the macrosomia funnel plot (p=0.58), but adjustment for publication bias with the trim and fill method suggests little impact on the strength of the association (from RR=0.47 to RR=0.49; 95% CI, 0.36-0.66). However, the small number of studies limited analysis of publication bias.

Quality and impact assessments

Tables 2 and 3 present information on the quality of the evidence found for adverse perinatal and maternal outcomes. We found high quality evidence for the reduction of macrosomia and LGA birth, and low quality evidence for shoulder dystocia, due to the small number of events. Number needed to treat (NNT) to prevent one outcome was 11.4 (95% CI, 9.1-17.3) for macrosomia, 12.2 (95% CI, 9.9-18.1) for LGA birth and 48.8 (36.9-120) for dystocia. Regarding maternal outcomes, we found moderate quality evidence for the reduction of preeclampsia and hypertensive disorders in pregnancy. The NNTs for these outcomes were 21.0 (95% CI, 15.1-43) and 18.1 (95% CI, 13.4 -34.2),

respectively. As can be seen from these tables, the remaining outcomes presented moderate to very low quality evidence, basically due to the small number of events reported.

DISCUSSION

Based on the findings of our systematic review of the literature, high quality evidence indicates that the treatment of GDM reduces macrosomia (RRR=53%; NNT, 11.4) and LGA birth (RRR=43%; NNT=12.2). We also found moderate quality evidence that GDM treatment reduces preeclampsia (RRR, 39%; NNT, 21) and hypertensive disorders in pregnancy (RRR=36%; NNT=18.1). Results were generally consistent across studies, despite the fact that the included trials were conducted over a span of over 40 years during which obstetric and metabolic treatments improved considerably and glycemic thresholds for initiating GDM treatment decreased. No significant reduction was seen for delivery by cesarean section, and trial sequential analysis considering a 20% risk reduction as clinically relevant, showed that an adequate sample size had been achieved. Treatment of GDM did not increase the risk for the two potential adverse effects evaluated, small for gestational age and preterm birth.

This is the largest (3157 women) systematic review assessing the effectiveness of GDM treatment (versus usual antenatal care) and the most comprehensive analysis of purported GDM outcomes conducted to date. To optimize comprehensiveness, we did not exclude studies due to language restrictions or publication date, and we searched for ongoing trials. Additionally, to be able to address relevant clinical outcomes such as perinatal mortality, we did not exclude older studies that used quasi-randomized allocation. Of note, our sensitivity analyses did not find evidence of inconsistency in this respect. Moreover, it is unlikely that new studies comparing GDM treatments with

conventional obstetric care will ever be conducted, at least within the larger range of hyperglycemia here analyzed.

Due to the small number of included studies and their large variety of diagnostic criteria (see Table 1), we were unable to summarize results separately for the individual diagnostic criteria used in each study. However, it should be noted that the ACHOIS study, which employed the WHO definition of GDM (75g OGTT; 2h PG ≥140 mg/dl), provides evidence that treatment based on this definition of GDM prevents macrosomia, LGA birth and hypertensive disorders in pregnancy. The remaining studies were generally based on a 100g OGTT, usually requiring two out of four abnormal values (fasting, 1h, 2h, 3h), and using different cutoffs. The recently proposed IADPSG 75g OGTT criteria require one abnormal value out of three (FPG ≥92 mg/dl; 1h ≥180 mg/dl; 2h ≥153 mg/dl),[3] defining a milder degree of hyperglycemia than that seen in most of the included trials. The Landon et al. trial[10] treated women with levels of glycemia most comparable to those defined by the IADPSG criteria: fasting plasma glucose values < 95 mg/dl, versus ≥92 mg/dl by the IADPSG criteria; plus two out of three post load abnormal values (1h ≥180 mg/dl; 2h ≥155 mg/dl; 3h ≥140 mg/dl).

Although the 1h and 2h cut points of Landon's trial are almost identical to those proposed by the IADPSG, the latter allow diagnosis of GDM based in only one of the three glucose values. Of note, the Landon et al. is the study which treated the mildest degree of hyperglycemia with only 7.6% of women in the treatment arm receiving insulin (Table 1). Treatment for GDM in this trial reduced the incidence of LGA birth, macrosomia, shoulder dystocia, preeclampsia, hypertensive disorders in pregnancy and cesarean section.

As the evidence here provided is derived from comparing global GDM treatment with usual antenatal care, it cannot address the specific benefits derived from different

components of GDM treatment, such as obstetric monitoring or individual interventions to manage hyperglycemia, nor the degree of glucose control achieved. Moreover, as diet and or physical activity were prescribed in all trials, it is not possible to separate their specific contribution from that of pharmacologic interventions. Insulin was the only glucose lowering pharmacological intervention used in the trials. In two of the largest and most recent trials, ACHOIS[9] and Landon et al.,[10] relatively few women (20% and 7.6% in the intervention group, respectively) received insulin. It is possible that non pharmacological interventions may have important roles in the prevention of adverse pregnancy outcomes that go beyond hyperglycemia, influencing pathways to disease associated with other risk factors associated with unhealthy diets and sedentary lifestyles such as obesity and excessive weight gain.[29–31] In fact, although a few women labeled as GDM may actually be cases of MODY (maturity-onset diabetes of the young) or type 1 diabetes, the vast majority have a condition with a pathophysiology that is very similar to type 2 diabetes and the metabolic syndrome, for which lifestyle interventions by themselves have been shown to be particularly effective both in terms of prevention and treatment.[32–34]

The clinical significance of reducing the adverse outcomes for which GDM treatment proved to be effective in this review merits discussion. Macrosomia may lead to significant obstetric and neonatal complications, such as shoulder dystocia, for which we found evidence supporting the benefit of treating GDM, as well as other complications which may require obstetric interventions or admission to neonatal intensive care unit.[35] Macrosomia or being LGA are also markers of altered fetal programming[36] which may increase the risk for future chronic complications of potentially greater relevance, such as childhood obesity, diabetes, metabolic syndrome, hypertension and cardiovascular morbidity.

The maternal outcomes prevented with GDM treatment (preeclampsia or hypertensive disorders in pregnancy), may also have short and long term benefits. Prevention of preeclampsia minimizes the risk of eclampsia, a life threatening condition associated with maternal and perinatal mortality and severe morbidity. Additionally, long term adverse effects of preeclampsia include increased risk for maternal cardiovascular disease[37] as well as long term adverse outcomes in infants of mothers with preeclampsia due to fetal growth restriction caused by reduced placental perfusion.[38]

Our results indicate that treatment of GDM is effective. Implications for specific diagnostic criteria are limited. Of note, most studies in this review used diagnostic criteria that identified cases of GDM of greater severity than most detected using the WHO or IADPSG criteria. One of the high quality studies utilized the WHO diagnostic criteria and found benefit for the treatment of GDM.[9] Another high quality study utilizing diagnostic criteria with cut points resembling those of the IADPSG and identifying milder glucose intolerance, also found that treatment of GDM is of benefit.[10] However, the generalizability of our findings on the benefits of treating milder cases of GDM, such as those diagnosed by the IADPSG criteria, is less clear. In fact, a recent cost-utility analysis indicates that screening based on the IADPSG-criteria, followed by treatment, is not cost effective unless long-term maternal benefits of diabetes prevention programs are considered.[39] Of note, treatment of milder forms of hyperglycemia (glucose intolerance according a 50g-1h glucose challenge test but not meeting GDM criteria by an OGTT) focusing on lifestyle modifications, glucose monitoring and occasional insulin therapy, was also found to be effective in the prevention of LGA birth and macrossomia.[40,41]

Our study has some limitations. First, the database generated lacked power to detect beneficial effects with respect to relevant outcomes such as perinatal mortality and admission to the intensive care unit; as well as potential adverse effects of GDM treatment

such as SGA birth. Analyses regarding information size indicate that the total number of women required to be randomized would range from 5500 for ICU admission to 40000 for perinatal mortality to detect, with adequate power, a 20% change in risk for these outcomes. Second, lack of adequate blinding for all trials may limit the validity of selected outcomes, particularly cesarean section. Third, most studies were conducted in high income countries, thus limiting the ability to generalize their results to other settings, especially given that intensive obstetric monitoring was part of the intervention in some studies.

In sum, our study adds important findings beyond those of two recent meta-analyses[11,12] on the subject. Due to its comprehensiveness and more thorough analyses, it provides more complete and precise estimates for the effects of treating GDM, and indicates that an adequate sample has been achieved to evaluate major outcomes, including preeclampsia. Additionally, it classifies the quality of the available evidence supporting GDM treatment for each outcome and highlights evidence for treatment based on the WHO and the IADPSG criteria. Given that randomized trials to assess the effectiveness of screening for GDM have not been performed, these findings provide important indirect support for such screening.

In conclusion, treatment of GDM is effective in reducing LGA birth, macrosomia, shoulder dystocia, preeclampsia and hypertensive disorders in pregnancy. The risk reduction for these outcomes is, in general, large, the number need to treat is low, and the quality of evidence is adequate, thus justifying treatment of GDM. No evidence was found suggesting important adverse effects of treatment. The data presented here cannot determine the extent to which these benefits accrue from pharmacologic interventions to reduce hyperglycemia or from lifestyle interventions which also affect other risk factors for these outcomes.

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M.F. wrote the protocol, researched and analyzed data and wrote the manuscript. J.T. and M.R.T researched data and reviewed the manuscript. L.F.A. researched data and edited the manuscript. E.R.W., S.C. and B.B.D. contributed to discussion and reviewed the manuscript. M.I.S. participated in all the aspects of the project and was the overall supervisor.

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Figure legends

Figure 1 – Effects of gestational diabetes treatment vs. usual antenatal care on perinatal outcomes

Figure 2 - Effects of gestational diabetes treatment vs. usual antenatal care on maternal outcomes

Supplementary Figure 1 - Flow diagram of literature search and study selection

Supplementary Figure 2 – Effects of gestational diabetes treatment vs. usual antenatal care on perinatal outcomes (detailed informations)

Supplementary Figure 3 – Effects of gestational diabetes treatment vs. usual antenatal care on maternal outcomes (detailed informations)

Supplementary Figure 4 – Sensitivity analysis excluding the quasi-randomized studies

Supplementary Figure 5 - Trial sequential analysis for outcomes with a greater number of events

Table 1. Characteristics of included studies comparing gestational diabetes treatment to usual antenatal care

Study	N	Ethnicity	Age mean ± sd	Screening test mg/dL	Diagnostic criteria for GDM mg/dL	Interventions in the experimental group	Insulin treatment in the experimental group (%)
ACHOIS 2005[9] Australia / UK	1000	White: 75% Asian: 16% Other: 8%	30.5 ± 5.5	Risk factors and 50g-1h ≥ 140	75g-OGTT 2hs ≥ 140	Diet Self glucose monitoring Insulin if needed	20%
Garner 1997[23] Canada	300	NR	30.7 ± 4.7	50g-1h ≥ 144	75g-OGTT 2h ≥ 135 (2nd trimester) 2h ≥ 173 (3rd trimester)	Diet Insulin if needed Bi-weekly biophysical profiles	24%
Landon 2009[10] USA	958	Black: 11% White: 25% Asian: 5% Hispanic: 57% Other: 1%	29.1 ± 5.7	50g-1h ≥ 135.	100g-OGTT F < 95 and 2 abnormal: 1h ≥ 180, 2h ≥ 155, 3h ≥ 140.	Diet Insulin if needed	7.6%
Langer 1989[24] USA	126	Black: 32% Hispanic: 33% Other: 35%	29.5 ± 5.5	50g-1h ≥ 130	100g OGTT 2 abnormal: F ≥ 105; 1h ≥ 190; 2h ≥ 165; 3h ≥ 145	Diet Insulin if needed	35%
Li 1987[25] Hong Kong	158	NR	28.3 ± 4.5	Risk factors.	100g OGTT- 2 abnormal: F ≥ 105; 1h ≥ 190; 2h ≥ 165; 3h ≥ 145	Diet Glucose monitoring	0%
O'Sullivan 1966[26,27] USA	615	NR	30.8	50g-1h ≥ 130 or history of previous pregnancies with related morbidity;	100g OGGT- 2 abnormal: F ≥ 110; 1h ≥ 170; 2h ≥ 120; 3h ≥ 110	Diet Insulin for all women	100%
O'Sullivan 1974[28] USA	241	NR	30	50g-1h ≥ 130	100g OGTT- 2 abnormal: F ≥ 90; 1h ≥ 165; 2h ≥ 145; 3h ≥ 125	Diet Insulin for all women	100%

Abbreviations: F – fasting; GDM – gestational diabetes melitus; N – number of patients evaluated; NR – not reported; OGTT – oral glucose tolerance test; sd – standard deviation.

Table 2. GRADE evaluation of specific treatment for gestational diabetes based on adverse perinatal outcomes

Population: women with GDM
Intervention: any kind of specific GDM treatment
Comparison: usual antenatal care
Outcome: adverse perinatal outcomes

	Design / sample	Quality assessment	RR (95% CI)	NNT (95% CI)	Quality	Importance
Macrosomia	Experimental - 6 studies; n=3315 ; 480 events	No serious limitations; no serious inconsistency; no serious indirectness; no serious imprecision; presence of large effect size with adequate sample size.	0.47 (0.34 – 0.65)	11.4 (9.1 – 17.3)	High + + + +	Critical
Large for gestational age birth	Experimental – 4 studies n = 2245; 333events	No serious limitations; no serious inconsistency; no serious indirectness; no serious imprecision.	0.57 (0.47 – 0.71)	12.2 (9.9 – 18,1)	High + + + +	Important
Shoulder dystocia	Experimental – 2 studies n = 1961; 58 events	No serious limitations; no serious inconsistency; no serious indirectness; very serious imprecision (small number of events)	0.41 (0.22 – 0.76)	48.8 (36,9 – 120)	Low + + ○ ○	Important
Perinatal mortality	Experimental - 7 studies; n=3396 ; 46 events	Serious limitations (inadequate allocation method for trials with more weigh); no serious inconsistency; serious indirectness (most events from old studies, when mortality rate was higher); very serious imprecision (small number of events)	0.62 (0.31 – 1.24)	Not significant	Very Low + ○ ○ ○	Critical
Neonatal ICU admission	Experimental – 2 studies n=1058; 98 events	No serious limitations; no serious inconsistency; no serious indirectness; very serious imprecision (small number of events)	0.75 (0.52 – 1.08)	Not significant	Low + + ○ ○	Critical
Birth trauma	Experimental – 2 studies n = 1961; 12 events	No serious limitations; no serious inconsistency; no serious indirectness; very serious imprecision (small number of events)	0.39 (0.11 – 1.35)	Not significant	Low + + ○ ○	Critical
Small for gestational age birth	Experimental – 3 studies n=2088; 145 events	No serious limitations; no serious inconsistency; no serious indirectness; serious imprecision (small number of events)	1.05 (0.77 – 1.44)	Not significant	Moderate + + + ○	Important
Preterm birth	Experimental – 3 studies n=1669; 156 events	No serious limitations; no serious inconsistency; serious indirectness (diverse study definition); serious imprecision (small number of events)	0.90 (0.67 – 1.21)	Not significant	Low + + ○ ○	Important
Congenital abnormalities	Experimental – 3 studies n=1068; 94 events	Serious limitations (inadequate allocation method for trials); no serious inconsistency; serious indirectness (lack of standardization for congenital abnormalities); very serious imprecision (small number of events)	0.81 (0.55 – 1.18)	Not significant	Very Low + ○ ○ ○	Critical
Hyperbilirubinemia	Experimental – 4 studies n =2323; 220 events	No serious limitations; no serious inconsistency; serious indirectness (different outcome definitions); serious imprecision (small number of events)	0.81 (0.63 – 1.04)	Not significant	Low + + ○ ○	Important
Neonatal hypoglycemia	Experimental – 4 studies n =2193; 222 events	No serious limitations; serious inconsistency (inconsistency dependent on the choice of the variance estimator in the random-effects model); serious indirectness (different outcome definitions); serious imprecision (small number of events)	1.16 (0.90 – 1.49)	Not significant	Very Low + ○ ○ ○	Important
Respiratory distress syndrome	Experimental – 2 studies n = 1962; 68 events	No serious limitations; serious inconsistency (heterogeneity between studies); no serious indirectness; very serious imprecision (small number of events)	1.05 (0.48 – 2.28)	Not significant	Very Low + ○ ○ ○	Critical

Abbreviations: CI – confidence interval; n – number of patients evaluated; NNT – number needed to treat; RR – relative risk.

Table 3. GRADE Evaluation of specific treatment for Gestational Diabetes based on adverse maternal outcomes

Population: women with GDM
Intervention: any kind of specific GDM treatment
Comparison: usual antenatal care
Outcome: adverse maternal outcomes

	Design / sample	Quality assessment	RR (95% CI)	NNT (95% CI)	Quality	Importance
Preeclampsia	Experimental - 2 studies; n=1931; 188 events	No serious limitations; no serious inconsistency; no serious indirectness; serious imprecision (small number of events)	0.61 (0.46 – 0.81)	21 (15.1 – 43)	Moderate + + + ○	Critical
Hypertensive disorders in pregnancy	Experimental - 3 studies; n=2057; 259 events	No serious limitations; no serious inconsistency; serious indirectness (diverse study definition); no serious imprecision;	0.64 (0.51 – 0.81)	18.1 (13.4 – 34.2)	Moderate + + + ○	Important
Caesarean section	Experimental - 5 studies; n=2514; 718 events	Serious limitations (unblinded trials or selective blinding for control group); no serious inconsistency; no serious indirectness; no serious imprecision.	0.90 (0.78 – 1.05)	Not significant	Moderate + + + ○	Important
Diabetes mellitus later in life	Experimental – 1 study n=711; 217 events	Serious limitations (inadequate allocation method for trials); no serious inconsistency; no serious indirectness; serious imprecision (small number of events)	0.98 (0.79 – 1.21)	Not significant	Low + + ○ ○	Critical

Abbreviations: CI – confidence interval; n – number of patients evaluated; NNT – number needed to treat; RR – relative risk.

Figure 1. Effects of gestational diabetes treatment vs. usual antenatal care on perinatal outcomes

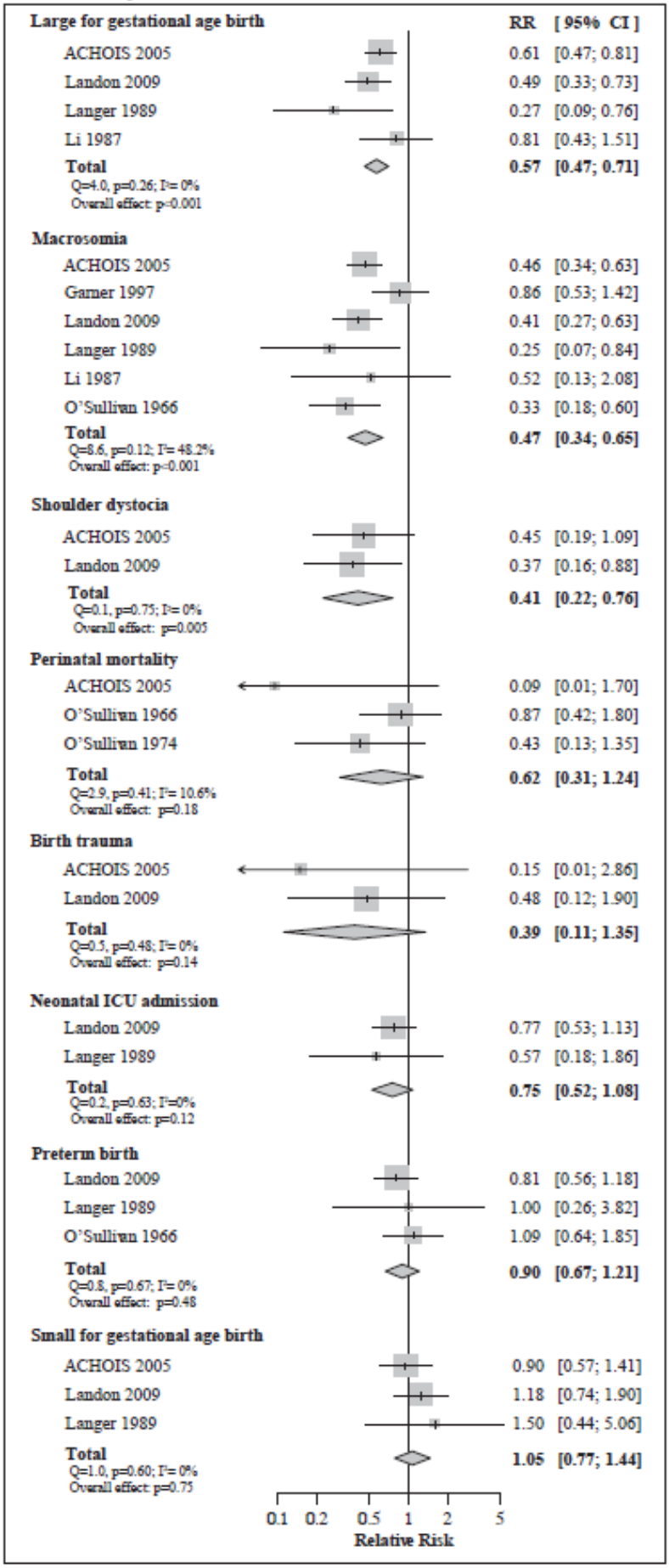
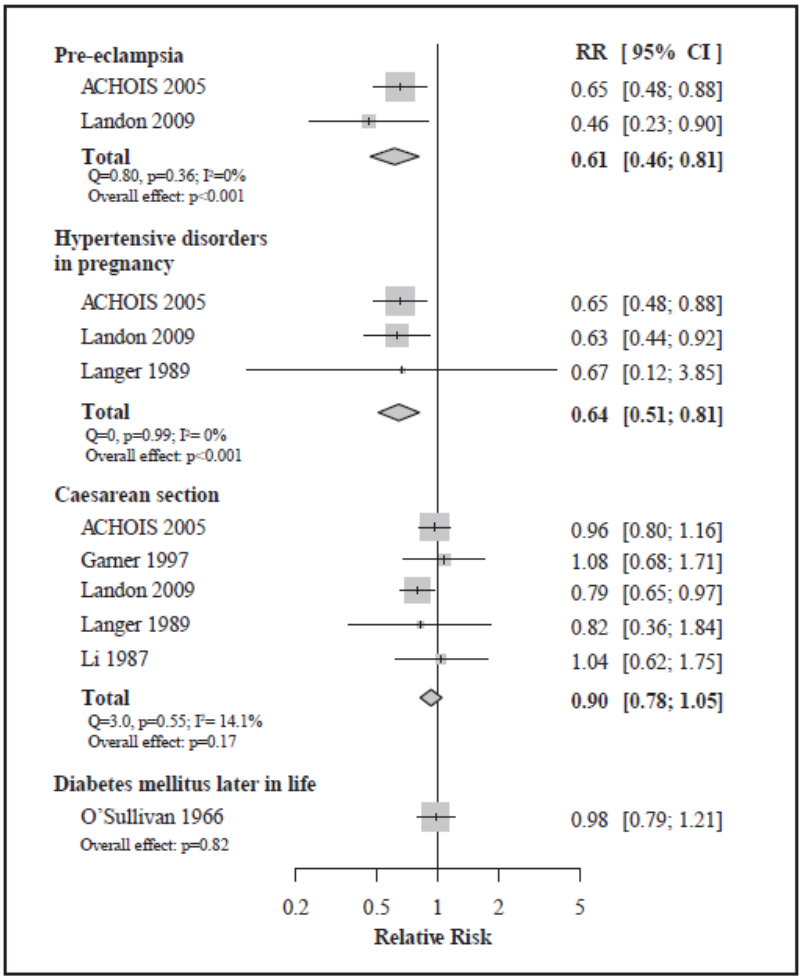
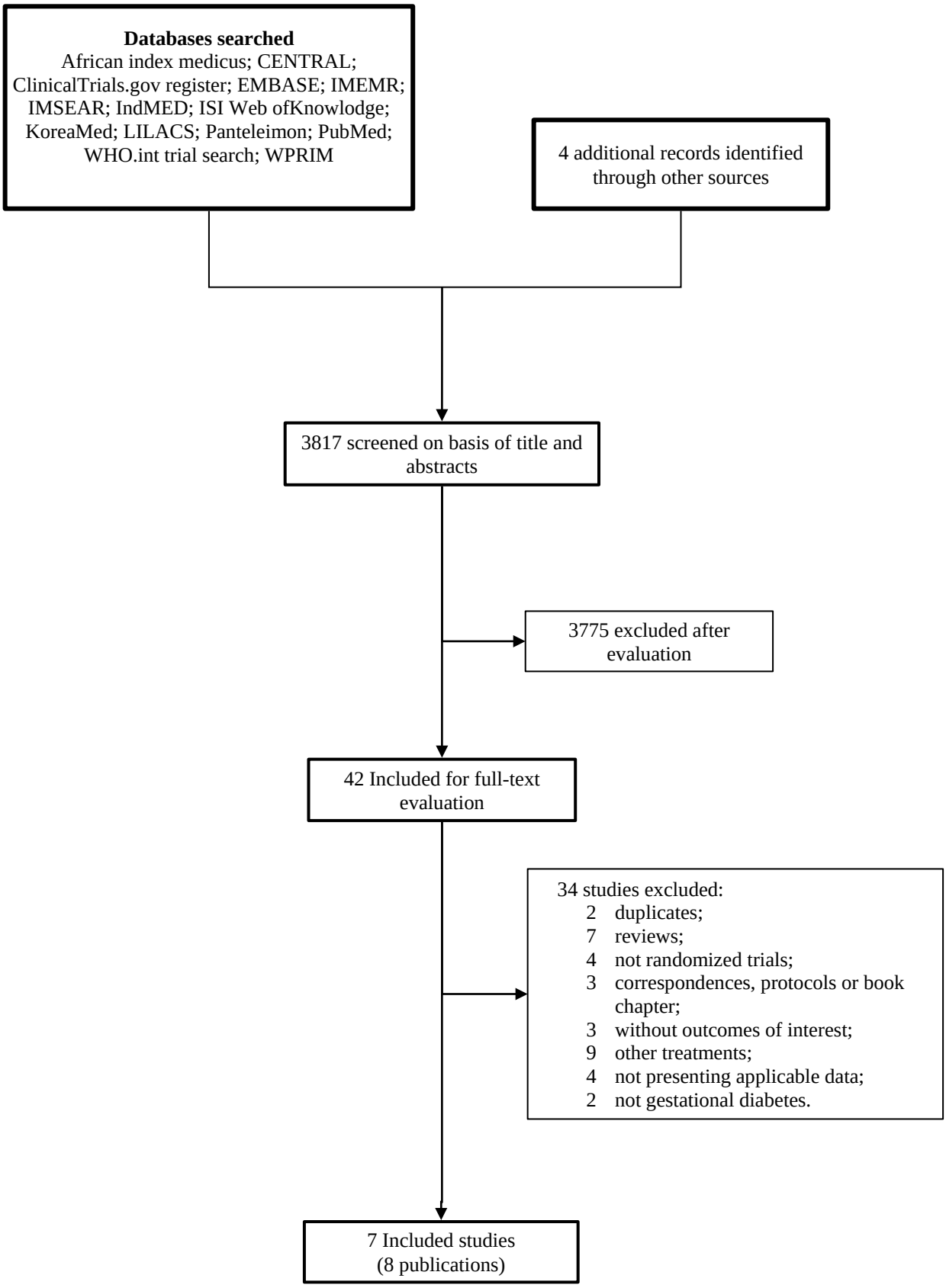


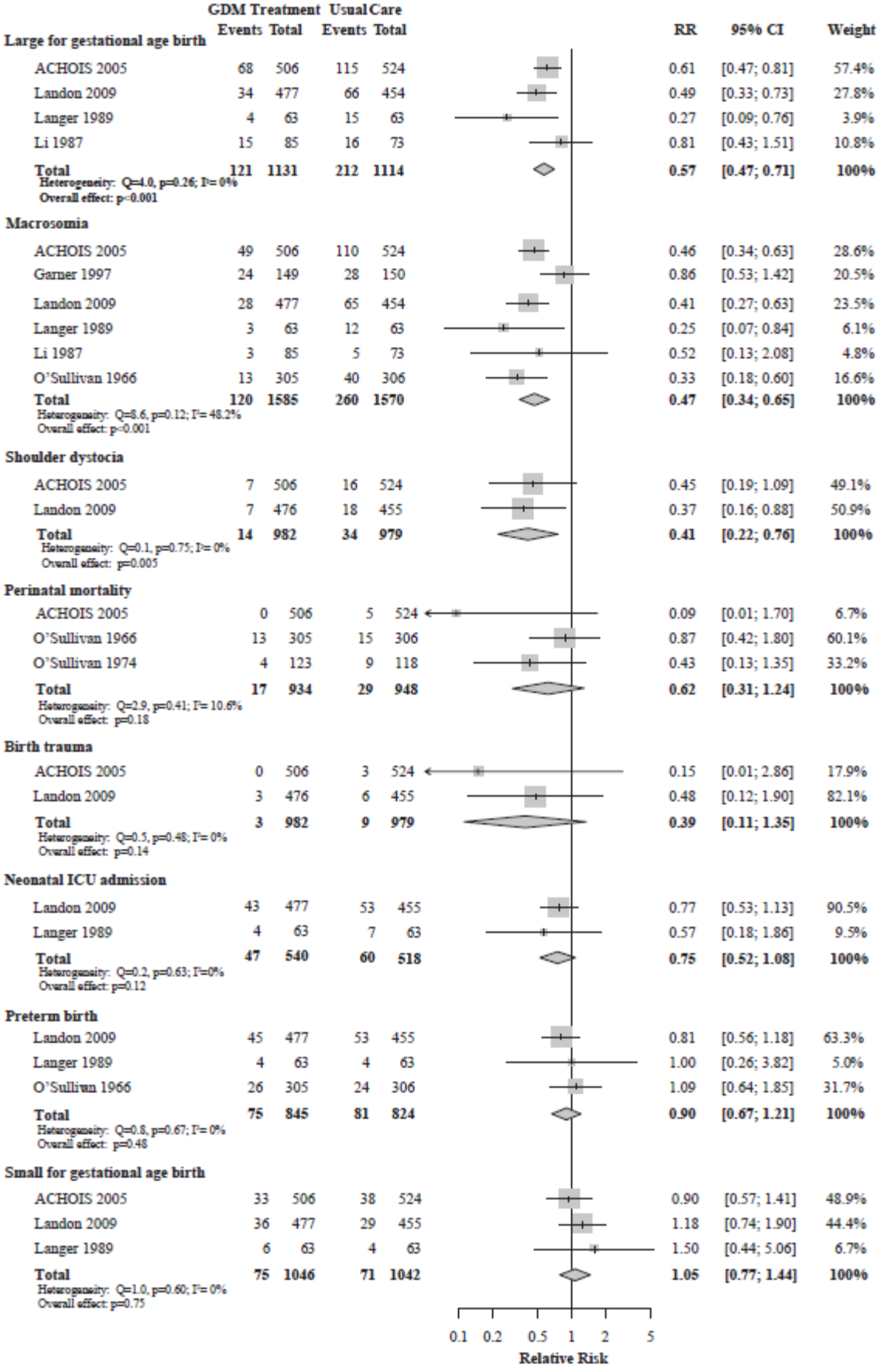
Figure 2. Effects of gestational diabetes treatment vs. usual antenatal care on maternal outcomes



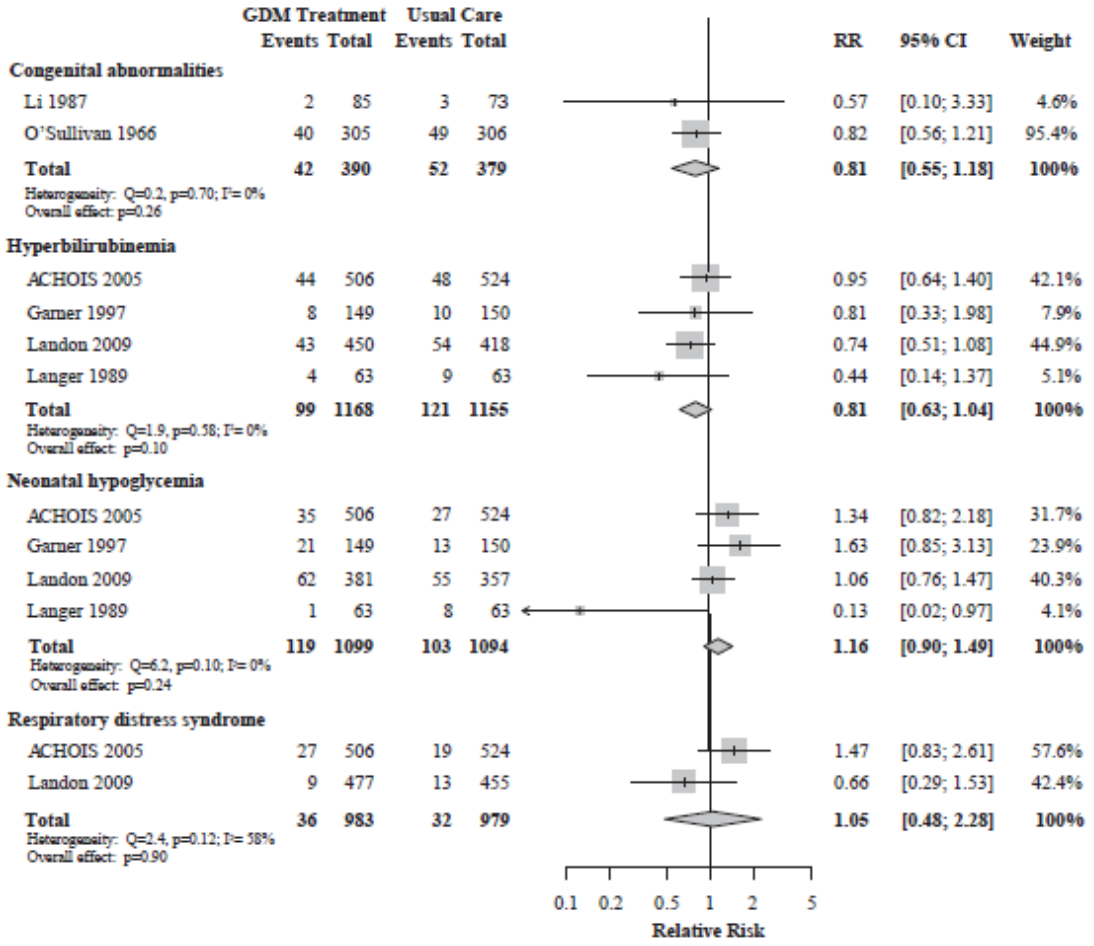
Supplementary Figure 1. Flow diagram of literature search and study selection



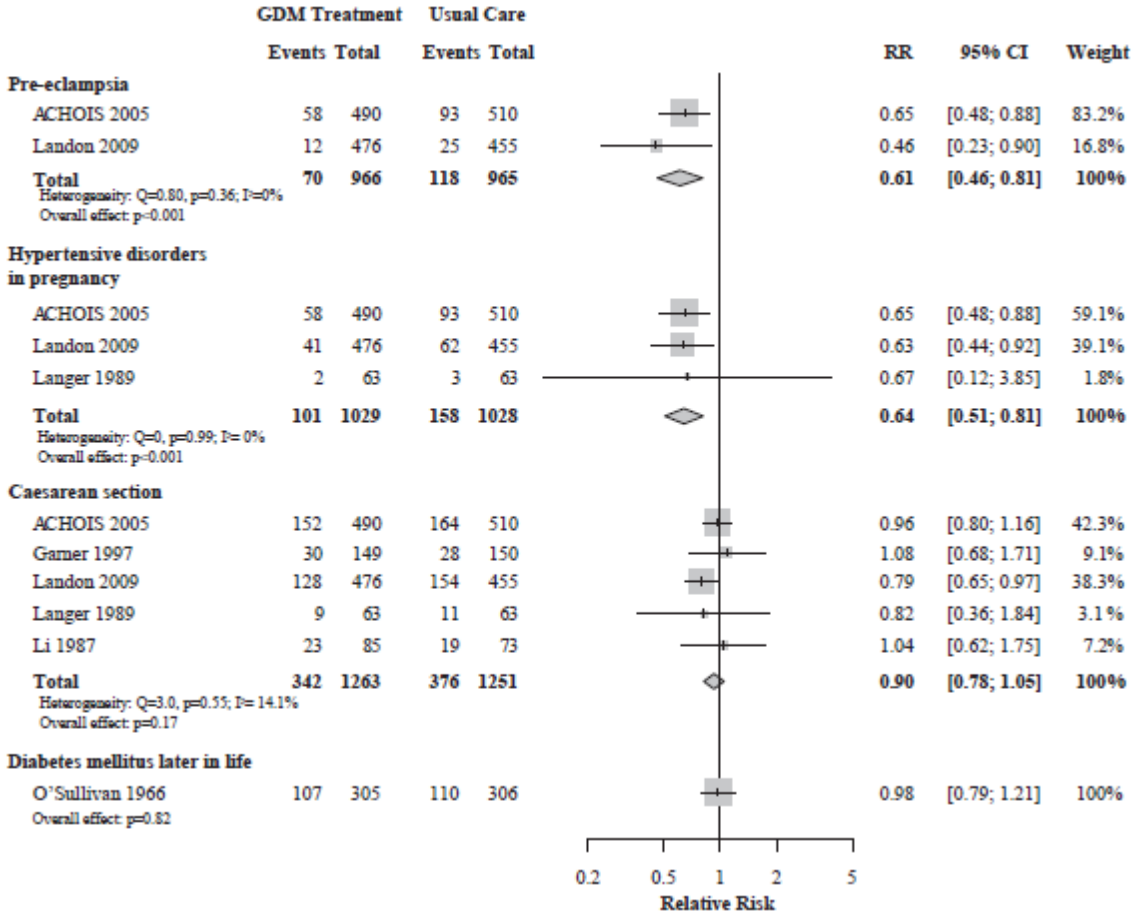
Supplementary Figure 2. Effects of gestational diabetes treatment vs. usual antenatal care on perinatal outcomes (detailed informations)



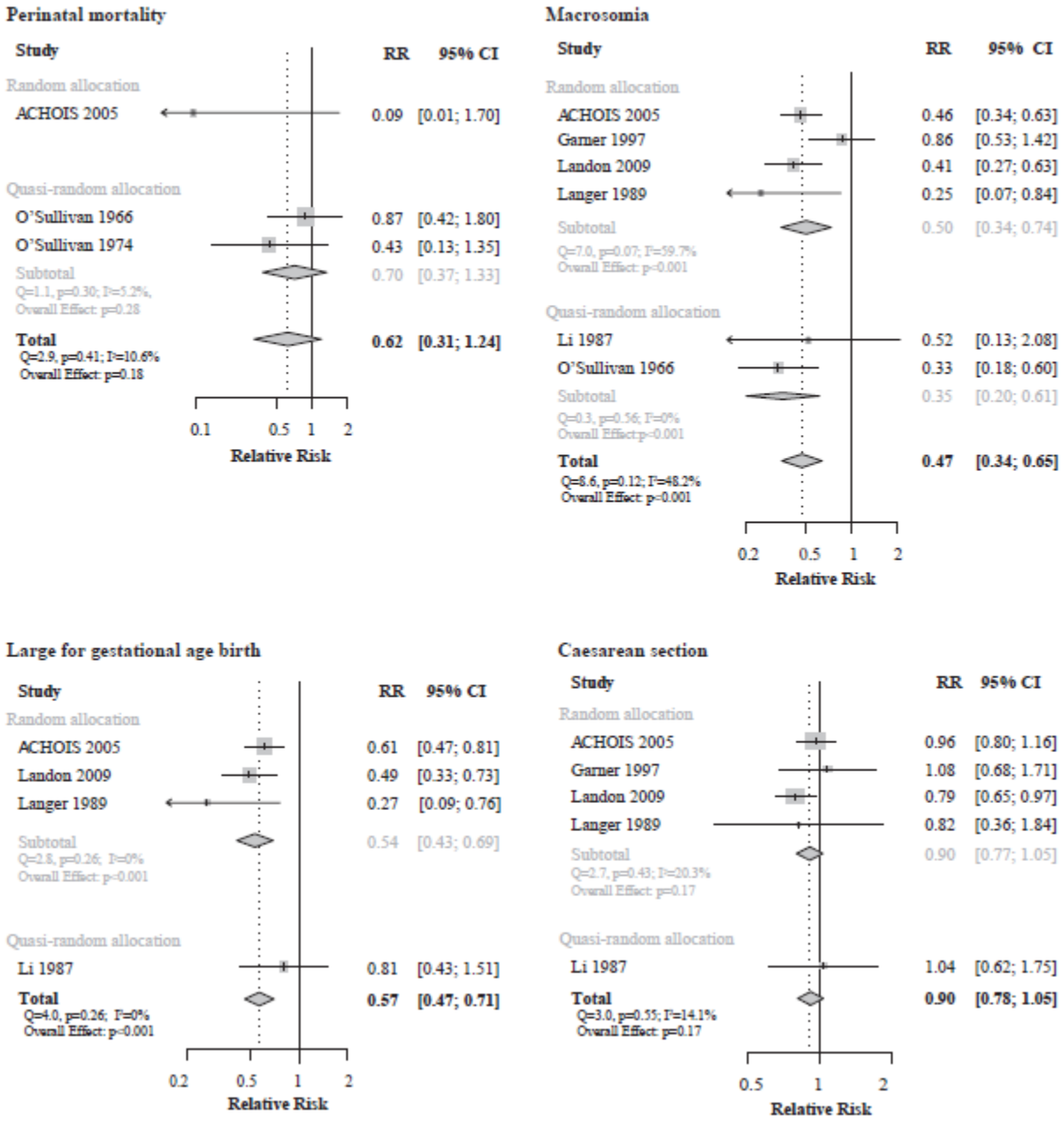
Supplementary Figure 2 (cont.) Effects of gestational diabetes treatment vs. usual antenatal care on additional perinatal outcomes (detailed informations)



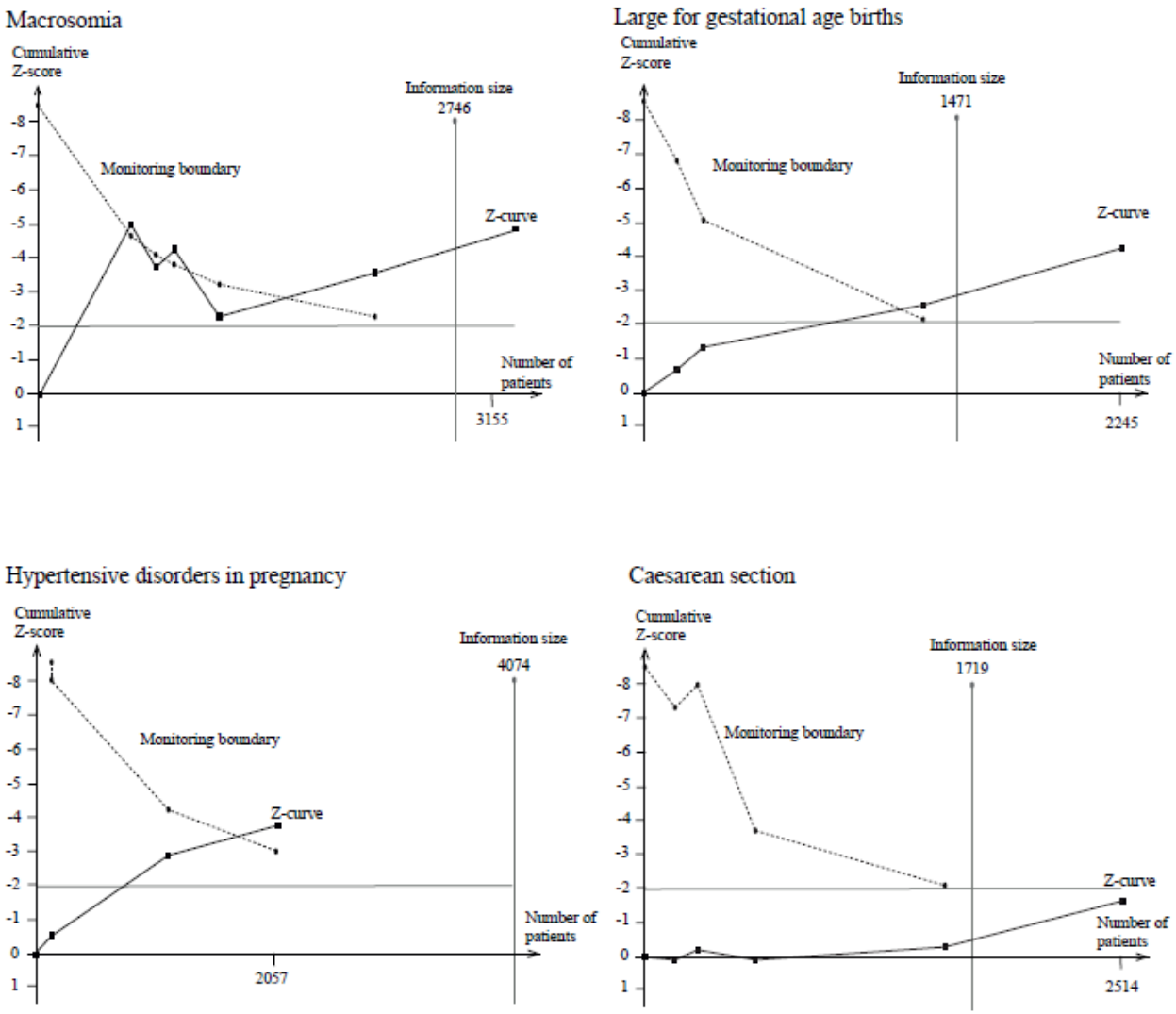
Supplementary Figure 3. Effects of gestational diabetes treatment vs. usual antenatal care on maternal outcomes



Supplementary Figure 4. Sensitivity analysis excluding the quasi randomized studies



Supplementary Figure 5. Trial sequential analysis for outcomes with a greater number of events



Footnotes:
Alpha 0.05; beta 0.8; model variance based heterogeneity correction (DerSimonean and Laird random effects model). Incidence in the control group and relative risk reduction assumed, respectively as 15% and 35% for macrosomia, 20% and 25% for Large for gestational age birth, 15% and 20% for hypertensive disorders in pregnancy, 30% and 20% for caesarean section.
The Z-curve permits assessment of statistical significance, according to the Wald-test, with z=1.96, corresponding to an alpha=0.05; each point in the Z-curve represents a new study added in the cumulative meta-analysis, according to their publication order. Low risk for random error is present when the Z-curve crosses the monitoring boundary curve or the information size line

Supplementary Table 1. Search strategies for electronic databases

Engine	Strategy
African Index Medicus	gestation$ AND diabet$
CENTRAL (The Cochrane Central Register of Controlled Trials)	#1 MeSH descriptor Diabetes Mellitus explode all trees #2 MeSH descriptor Fetal Macrosomia explode all trees #3 diabet* in Clinical Trials #4 (#1 OR #2 OR #3) #5 gestation* #6 pregnan* #7 MeSH descriptor Pregnancy explode all trees #8 (#5 OR #6 OR #7) #9 MeSH descriptor Diabetes, Gestational explode all trees #10 (#4 AND #8) #11 (#9 OR #10) Clinical Trials
EMBASE	#1 'diabetes mellitus'/exp #2 macrosomi* #3 diabet* #4 #1 OR #2 OR #3 #5 gestation* #6 pregnan* #7 'gestation'/exp #8 #5 OR #6 OR #7 #9 'gestational diabetes mellitus'/exp #10 #4 AND #8 OR #9 #11 doubl* OR singl* OR tripl* OR trebl* AND (blind* OR mask*) #12 random* #13 'randomized controlled trial'/exp #14 #11 OR #12 OR #13 #15 #10 AND #14
IMEMR (Index Medicus for the Eastern Mediterranean Region)	gestation$ and diabet$ [KeyWords] and random$ [KeyWords]
IMSEAR (Index Medicus for the South-East Asia Region)	(((((((blind$ OR Mask$)) AND (doubl$ OR singl$ OR tripl$ OR trebl$))) OR (Randomized controlled trial) OR (random$))) AND (gestational diabetes))
IndMED	(gestational diabetes) or ((gestation$ OR pregnan$) AND (diabet$ OR Macrosomi$)) and (random$ OR blind$ OR mask$)
ISI Web of Knowlodge	#1 Topic=(diabetes mellitus) #2 TS=(macrosomi*) #3 TS=(diabet*) #4 #1 OR #2 OR #3 #5 TS=(gestation*) #6 TS=(pregnan*) #7 #6 OR #5 #8 TS=(gestational diabetes mellitus) #9 #7 OR #8 #10 #4 AND #9 #11 Topic=(doubl* OR singl* OR tripl* OR trebl* AND (blind* OR mask*)) #12 TS=(random*) #13 TS=(randomized controlled trial) #14 #11 OR #12 OR #13 #15 #10 AND #14

KoreaMed	gestation* [ALL] AND diabet* [ALL] AND random* [ALL]
LILACS (Latin American and the Caribbean)	"DIABETES gestacional" or "DIABETES induzida por gravidez" or "DIABETES mellitus gestacional" [Descritor de assunto] or (macrosomi$ OR diabet$) AND (gestation$ OR pregnan$) [Palavras] and ((doubl$ OR singl$ OR tripl$ OR trebl$) AND (blind$ OR mask$)) OR (random$) [Palavras]
Panteleimon	#1 gestation #2 pregnancy #3 diabetes #4 #1 OR #2 #5 #3 AND #4 #6 random #7 #5 AND #6
PubMed	#1 Search "Diabetes Mellitus"[Mesh] #2 Search macrosomi* #3 Search diabet* #4 Search #1 OR #2 OR #3 #5 Search gestation* #6 Search pregnan* #7 Search "Pregnancy"[Mesh] #8 Search #5 OR #6 or #7 #9 Search "Diabetes, Gestational"[Mesh] #10 Search #4 and #8 #11 Search #9 or #10 #12 Search doubl* OR singl* OR tripl* OR trebl* AND (blind* OR mask*) #13 Search random* #14 Search "Randomized Controlled Trial" [Publication Type] OR "Randomi Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] #15 Search ((#12) OR #13) OR #14 #16 Search (#11) AND #15
WPRIM (Western Pacific Region Index Medicus)	#1 Default:gestation or Default:pregnancy #2 Default:diabetes mellitus or Default:diabetes or Default:macrosomic #3 #1 AND #2 #4 gestational diabetes mellitus #5 #3 OR #4 #6 randomized controlled trial #7 Default:double OR single OR triple and Default:blind OR mask #8 #5 and #6 and #7

Supplementary Table 2. Studies excluded and reasons for exclusion after full-text evaluation

Study	Reason
Alwan 2009[1]	Review
Athukorala 2007[2]	Without outcomes of interest
Beucher 2010[3]	Review
Bonomo 2004[4]	Other treatments
Bonomo 2005[5]	Not gestational diabetes
Coustan 2010[6]	Review
Coustan 1978[7]	Not randomized trial
Durnwald 2011[8]	Without outcomes of interest
Garcia-Patterson 2002[9]	Correspondence
Heller 2010[10]	Not gestational diabetes
Holmes 2004[11]	Not presenting applicable data
Hopp 1996[12]	Other treatments
Jovanovic-Peterson 1993[13]	Not presenting applicable data
Kjos 2001[14]	Other treatments
Landon 2008[15]	Duplicate
Landon 2007[16]	Duplicate
Landon 2002[17]	Protocol
Li 1987[18]	Not randomized trial
Li 1999[19]	Not randomized trial
Mathiesen 2008[20]	Review
Moses 2009[21]	Other treatments
O`Sullivan 1975[22]	Book chapter
O`Sullivan 1973[23]	Not presenting applicable data
O`Sullivan 1971[24]	Without outcomes of interest
Perez-Ferre 2010[25]	Other treatments
Persson 1985[26]	Other treatments
Peterson 1995[27]	Not presenting applicable data
Poyhonen-Alho 2002[28]	Other treatments
Simmons 1997[29]	Not randomized trial
Thompson 1990[30]	Other treatments
Tuffnell 2003[31]	Review
Turok 2003[32]	Review
Yang 2003[33]	Other treatments
Zera 2010[34]	Review

Supplementary Table 3. Assessment of risk of bias in included studies

Study	Sequence generation	Allocation Concealment	Blinding	Outcome data	Comments
ACHOIS 2005[35]	Low	Low	High	Low	Patients and caregivers blinded to OGTT results in the control group
Garner 1997[36]	Low	Uncertain	High	Low	Caregivers blinded to glucose monitoring tests in the control group. 10.7% of control group participants received treatment
Landon 2009[37]	Low	Low	High	Low	Patients and caregivers blinded to OGTT results in the control group
Langer 1989[38]	Uncertain	Uncertain	High	Low	None
Li 1987[39]	High	High	High	High	Allocation method based on alternation.
O'Sullivan 1966[40,41]	High	High	High	Uncertain	Allocation method probably based on alternation. Flowchart unclear
O'Sullivan 1974[42]	High	High	High	Uncertain	Allocation method based on alternation. Flowchart unclear

Abbreviation: OGTT – oral glucose tolerance test.
Risk of bias assessment according to Cochrane Handbook for Systematic Reviews of Interventions

Supplementary Table 4. Sensitivity analysis: effect of different variance estimators in the effect and inconsistence of gestational diabetes treatment vs. usual antenatal care on perinatal and maternal outcomes

	REML		ML		Empirical Bayes		Sidik-Jonkman		DerSimonean and Laird		Fixed effects model	
	RR	I^2	RR	I^2	RR	I^2	RR	I^2	RR	I^2	RR	I^2
PERINATAL OUTCOMES												
Macrosomia	0.47 (0.33-0.65)	48%	0.47 (0.36-0.62)	31%	0.47 (0.34-0.64)	43%	0.46 (0.33-0.66)	55%	0.47 (0.34-0.64)	42%	0.47 (0.39-0.58)	-
LGA birth	0.57 (0.47-0.71)	0%	0.57 (0.47-0.71)	0%	0.56 (0.41-0.76)	40%	0.55 (0.36-0.83)	63%	0.57 (0.43-0.74)	25%	0.57 (0.47-0.71)	-
Shoulder dystocia	0.41 (0.22-0.76)	0%	0.41 (0.22-0.76)	0%	0.41 (0.22-0.76)	0%	0.41 (0.22-0.76)	0%	0.41 (0.22-0.76)	0%	0.41 (0.22-0.76)	-
Perinatal mortality	0.59 (0.27-1.28)	22%	0.65 (0.36-1.19)	0%	0.56 (0.23-1.34)	35%	0.50 (0.16-1.56)	56%	0.57 (0.25-1.32)	30%	0.65 (0.36-1.19)	-
Neonatal ICU admission	0.75 (0.52-1.08)	0%	0.75 (0.52-1.08)	0%	0.75 (0.52-1.08)	0%	0.75 (0.51-1.10)	2%	0.75 (0.52-1.08)	0%	0.75 (0.52-1.08)	-
Congenital abnormalities	0.81 (0.55-1.18)	0%	0.81 (0.55-1.18)	0%	0.81 (0.55-1.18)	0%	0.80 (0.54-1.20)	1%	0.81 (0.55-1.18)	0%	0.81 (0.55-1.18)	-
Birth trauma	0.39 (0.11-1.35)	0%	0.39 (0.11-1.35)	0%	0.39 (0.11-1.35)	0%	0.37 (0.09-1.50)	9%	0.39 (0.11-1.35)	0%	0.39 (0.11-1.35)	-
Hyperbilirubinemia	0.81 (0.63-1.04)	0%	0.81 (0.63-1.04)	0%	0.81 (0.63-1.04)	0%	0.79 (0.57-1.10)	27%	0.81 (0.63-1.04)	0%	0.81 (0.63-1.04)	-
Respiratory distress syndrome	1.05 (0.48-2.27)	58%	1.13 (0.70-1.85)	5%	1.05 (0.48-2.28)	58%	1.05 (0.49-2.25)	56%	1.05 (0.48-2.27)	58%	1.04 (0.71-1.83)	-
SGA birth	1.05 (0.77-1.44)	0%	1.05 (0.77-1.44)	0%	1.05 (0.77-1.44)	0%	1.06 (0.74-1.50)	14%	1.05 (0.77-1.44)	0%	1.05 (0.77-1.44)	-
Neonatal hypoglycemia	1.16 (0.90-1.49)	0%	1.16 (0.90-1.49)	0%	1.00 (0.42-2.39)	88%	0.96 (0.36-2.57)	90%	1.16 (0.75-1.78)	52%	1.16 (0.75-1.78)	-
Preterm birth	0.90 (0.67-1.21)	0%	0.90 (0.67-1.21)	0%	0.90 (0.67-1.21)	0%	0.90 (0.66-1.24)	5%	0.90 (0.67-1.21)	0%	0.90 (0.67-1.21)	-
MATERNAL OUTCOMES												
Hypertensive disorders in pregnancy	0.64 (0.51-0.81)	0%	0.64 (0.51-0.81)	0%	0.64 (0.51-0.81)	0%	0.64 (0.51-0.81)	0%	0.64 (0.51-0.81)	0%	0.64 (0.51-0.81)	-
Pre-eclampsia	0.61 (0.46-0.81)	0%	0.61 (0.46-0.81)	0%	0.61 (0.46-0.81)	0%	0.60 (0.42-0.85)	20%	0.61 (0.46-0.81)	0%	0.61 (0.46-0.81)	-
Caesarean section	0.90 (0.78-1.05)	14%	0.90 (0.78-1.02)	0%	0.90 (0.78-1.02)	0%	0.91 (0.78-1.06)	19%	0.90 (0.78-1.02)	0%	0.90 (0.78-1.02)	-

Abbreviations: ICU – intensive care unit; LGA – large for gestational age; ML – maximum likelihood; REML –restricted maximum likelihood; SGA – small for gestational age

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7. ARTIGO 2 – IMPACTO DO RASTREAMENTO DO DIABETES GESTACIONAL

Impact of Gestational Diabetes Mellitus Screening Strategies on Perinatal Outcomes: a Simulation Study

[Impacto das Estratégias de Rastreamento do Diabetes Mellitus Gestacional em Desfechos Perinatais: Estudo de Simulação]

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SUMÁRIO - IMPACTO DAS ESTRATÉGIAS DE RASTREAMENTO DO DIABETES MELLITUS GESTACIONAL EM DESFECHOS PERINATAIS: ESTUDO DE SIMULAÇÃO

INTRODUÇÃO

Diabetes mellitus gestacional (DMG) é intolerância aos carboidratos, de intensidade variável, e com diagnóstico durante a gestação. O DMG é geralmente assintomático e detectado através de rastreamento sistemático após a 24ª semana de gestação. Não há estudos prospectivos adequados avaliando o impacto das estratégias de rastreamento do DMG; as recomendações são baseadas no potencial efeito adverso da hiperglicemia e na efetividade do tratamento em prevenir estes eventos.

Atualmente os principais critérios diagnósticos para o DMG são os recomendados pela Organização Mundial de Saúde (OMS) e pela *International Association of Diabetes in Pregnancy Study Groups* (IADPSG). Ambos são efetivos em classificar mulheres em risco aumentado de desenvolver eventos adversos perinatais, como pré-eclampsia, nascidos grandes para a idade gestacional (GIG) e necessidade de parto cesáreo.

O objetivo do presente estudo é avaliar o impacto de programas de rastreamento universal aplicando os critérios diagnósticos da OMS e da IADPSG.

MÉTODOS

Delineamento: Estudo de simulação, modelando coorte hipotética de gestantes submetidas a diferentes estratégias de rastreamento para o DMG. Os parâmetros do modelo foram obtidos através de revisões sistemáticas recentes.

Descrição do modelo de simulação:

População: gestantes sem diagnóstico de diabetes mellitus. A prevalência estimada de DMG nessa população é de 10% de acordo com o critério da OMS, sendo considerado um aumento da ordem de 50% na prevalência com o critério da IADPSG.

Intervenção: aplicação do teste oral de tolerância a glicose, com subsequente tratamento específico das gestantes diagnosticadas com DMG.

Grupos de comparação: (1) ausência de rastreamento; (2) rastreamento universal, com diagnóstico realizado pelo critério da OMS de 1999 e (3) rastreamento universal, com diagnóstico realizado pelo critério da IADPSG.

Desfechos: avaliada a incidência de nascidos GIG, de pré-eclampsia e de parto cesáreo.

Análise estatística: abordagem Bayeseana, com realização de simulações de Monte Carlo. Resultados apresentados como redução absoluta da incidência e número necessário para rastrear (NNS), com intervalos de credibilidade (IC) de 95%. A análise foi realizada com o software *R* versão 2.11.1, pacote *Boa.*

RESULTADOS

Comparado com ausência de rastreamento, a estratégia de rastreamento universal aplicando o critério da OMS reduziu a incidência de nascidos GIG em 0,53% (95%IC 0,37 – 0,74%; NNS = 189) e de pré-eclampsia em 0,27% (95%IC 0,10 – 0,45%; NNS = 376). A estratégia de rastreamento universal aplicando o critério da IADPSG reduziu a incidência de nascidos GIG em 0,85% (95%IC 0,54 – 1,29%; NNS = 117) e de pré-eclampsia em 0,39% (95%IC 0,15 – 0,65%; NNS = 257). Não ouve redução estatisticamente significativa na taxa de partos cesáreos

A estratégia de rastreamento baseadas no critério da IADPSG, quando comparada ao da OMS, reduziu a incidência de nascidos GIG em 0,32% (95%IC 0,09 – 0,63%; NNS = 309) e de pré-eclampsia em 0,12% (95%IC 0,01 – 0,25%; NNS = 808).

Dada a natureza das comparações indiretas realizadas através do modelo de simulação, a qualidade da evidência foi considerada muito baixa de acordo com a abordagem do *Grading of Recommendations Assessment, Development and Evaluation* (GRADE).

CONCLUSÕES

O rastreamento universal possui impacto modesto na prevenção de eventos adversos perinatais. A estratégia baseada no critério diagnóstico proposto pela IADPSG preveniu um maior número de eventos adversos, contudo classificou um maior número de mulheres como acometidas pelo DMG.

Frente ao benefício discreto apresentado, e considerando a potencial carga de trabalho ao serviços de saúde que as estratégias de rastreamento deverão gerar, custos e utilização de recursos devem ser considerados a nível local para a formulação de recomendações relativas ao rastreamento do DMG.

Impact of Gestational Diabetes Mellitus Screening Strategies on Perinatal Outcomes: a Simulation Study

Short title: Impact of GDM Screening Strategies

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ABSTRACT

AIMS: To evaluate the impact on perinatal outcomes of universal gestational diabetes (GDM) screening based on 1999 WHO and IADPSG diagnostic criteria; to assess the quality of the evidence (GRADE) to support GDM screening.

METHODS: Simulation of a hypothetical cohort of community-based pregnant women with 10% GDM prevalence (1999 WHO). Most parameters were obtained from recent systematic reviews.

RESULTS: Compared to no screening, screening based on 1999 WHO criteria (followed by treatment) reduced the incidence of large for gestational age (LGA) neonates by 0.53% (95% CI 0.37% - 0.74%; NNS=189) and of preeclampsia by 0.27% (0.10% - 0.45%; NNS=376). Screening based on IADPSG criteria reduced incidences by 0.85% (0.54% – 1.29%; NNS=117) and by 0.39% (0.15% – 0.65%; NNS=257), respectively. Compared to screening based on 1999 WHO criteria, screening with IADPSG criteria reduced the incidence of LGA by 0.32% (0.09% – 0.63%; NNS=309) and of preeclampsia by 0.12% (0.01% – 0.25; NNS=808). The quality of evidence for both screening approaches is very low.

CONCLUSIONS: Universal screening for GDM has only a modest impact on pregnancy outcomes. The impact of screening based on IADPSG (vs. 1999 WHO) criteria is slightly larger. However, costs and resources should also be considered in local selection of a screening approach.

Key words

Gestational Diabetes Mellitus, Screening, IADPSG, Evidence-Based Medicine, Simulation

INTRODUCTION

Gestational diabetes mellitus (GDM) has been defined as glucose intolerance of variable severity with onset or first recognition during pregnancy.[1,2] Although this definition has been largely accepted, the precise level of glucose intolerance characterizing GDM has been controversial over the last three decades.

Currently, the main diagnostic criteria for GDM are those which have been recommended by the World Health Organization (WHO) in 1999 and those recently proposed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG). Both diagnostic criteria are based on a 2h 75g OGTT. In their 1999 Report, the WHO reiterated their criteria of classifying GDM with a 2h plasma glucose ≥7.8 mmol/l (or 140 mg/dl).[3] The IADPSG criteria, derived from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study,[4] classify as GDM women with elevated values at any of the following three moments: a fasting glucose ≥ 5.1 mmol/L (92 mg/dl), a one hour result of ≥ 10.0 mmol/L (180 mg/dl), or a two hour result of ≥ 8.5 mmol/L (153 mg/dl). Both criteria predict important adverse outcomes, such as large for gestational age (LGA) neonates and preeclampsia.[4,5]

Although moderate to high quality evidence supports treatment of GDM,[6–8] prospective studies comparing outcomes in women screened versus not screened for GDM have not been undertaken. Nonetheless, screening asymptomatic pregnant women for GDM is a standard procedure in most parts of the world. The increasing prevalence of GDM, which probably results from the obesity epidemic;[9] the documented increased risk of adverse pregnancy outcomes with GDM;[5] and the effective reduction of this risk with treatment[8] have stimulated medical associations to promote screening programs. In so doing, the IADPSG criteria, which define a milder and much more prevalent hyperglycaemia, are gaining increasing acceptance.[10]

Within this scenario, evaluation of the impact of detecting and treating GDM is needed. In the absence of prospective controlled evaluations, one possibility is to model the impact of screening

strategies by simulating, with the best possible existing data, the outcomes of a hypothetical cohort of women, when screened and not screened.

Our aim is thus to evaluate the impact of universal screening based on the 1999 WHO and IADPSG diagnostic criteria in a simulation cohort, combining data from observational and experimental studies available in the literature. As part of this process, we also aim to assess the quality of the evidence for these screening approaches according to GRADE working group guidelines.[11,12]

METHODS

This study is part of the support material prepared for the WHO Consultation on the Diagnosis and Screening of Gestational Diabetes Mellitus. It is based on two systematic reviews, one which evaluated the association of GDM (as diagnosed by the 1999 WHO and by the IADPSG criteria) with adverse pregnancy outcomes[5] and the other which assessed the effectiveness of GDM treatment.[8] We created a model to simulate the experience of a cohort of pregnant women undergoing universal screening in order to assess the impact of these two diagnostic criteria. Additionally, we assessed the quality of the evidence for these two screening approaches according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.[11,12]

Model description

Population

Our hypothetical population consisted of all pregnant women attending general prenatal care services who lacked a previous diagnosis of diabetes mellitus outside of pregnancy.

Interventions (screening approaches)

The two universal screening approaches, evaluated against no screening, were:

- that based on the 1999 WHO criteria, and

- that based on the IADPSG criteria

Both assumed subsequent treatment of those detected. This treatment, as considered in the model, was by definition that employed in clinical trials producing the results summarized in the systematic review.[8] It thus involved lifestyle modifications, pharmacological intervention when deemed necessary, glucose monitoring and more intensive obstetric care.

Outcomes of interest

Robust data do not exist for most perinatal outcomes related to GDM. Thus, important outcomes such as maternal and perinatal mortality, birth trauma and shoulder dystocia were not evaluated. Although associations for macrosomia – an outcome commonly assessed in randomized trials of GDM – were available with respect to the 1999 WHO criteria, they were not included as data were sparse for the IADPSG criteria.[5]Adequate data were available for LGA neonates, preeclampsia and caesarean section, and thus simulations were performed only for these outcomes.

Model parameters

Parameters used in model simulations, including their most plausible values and the upper and lower limits used to estimate their population distributions, are presented in Table 1.

As the frequency of GDM varies worldwide, we considered a prevalence of 10% for the 1999 WHO criteria, which is close to that found in the HAPO study[4] and lies well within the range of published estimates (5 to 15%).[5] Less data are available to estimate the prevalence according to the IADPSG criteria. In large cohort studies, this prevalence was 25% to 130% greater[13,14] than that of the 1999 WHO criteria. We used a value of 50%, consistent with the findings of the HAPO study, for this model.[4,15]

We estimated that compliance would be 10% lower in this simulation of a real world setting than in the context of the clinical trials included in the systematic review.

We defined baseline risks of the three outcomes in women without GDM, using data obtained from a systematic review for the 1999 WHO criteria.[5] Rates expected for having an LGA neonate, preeclampsia and caesarean section in women without GDM were estimated at 9%, 4.5% and 18.5% respectively.[5] We calculated baseline risk for women with GDM according to the 1999 WHO criteria by combining these rates with relative risks (Table 1) for these outcomes obtained from the same source.[5]

To make results comparable across simulations of the different screening strategies, we fixed the baseline (without treatment) risk of the outcome being evaluated in the cohort to be equal across simulations, applying the following equation:

$$(1 - P_{WHO}) * R_{WHO\_negative} + P_{WHO} * R_{WHO\_positive} = (1 - P_{IADPSG}) * R_{IADPSG\_negative} + P_{IADPSG} * R_{IADPSG\_positive}$$

where,

P_{WHO}= prevalence of GDM according to the 1999 WHO criteria
P_{IADPSG} = prevalence of GDM according to the IADPSG criteria
$R_{WHO\_negative}$ = baseline risk of women without GDM based on the 1999 WHO criteria
$R_{WHO\_positive}$ = baseline risk of women with GDM based on the 1999 WHO criteria
$R_{IADPSG\_negative}$ = baseline risk of women without GDM based on the IADPSG criteria
$R_{IADPSG\_positive}$ = baseline risk of women with GDM based on the IADPSG criteria

To estimate baseline risks for screen negative and positive women according to the IADPSG strategy simulation, we then applied the following equation, which uses baseline risks for the 1999 WHO strategy. Considering that:

$$P_{IADPSG} = P_{WHO} * PR_{IADPSG\_WHO}$$
$$R_{IADPSG\_positive} = R_{IADPSG\_negative} * RR_{IADPSG}$$
$$R_{WHO\_positive} = R_{WHO\_negative} * RR_{WHO}$$

then

$$R_{IADPSG\_negative} = \frac{(P_{WHO} * R_{WHO\_negative} * RR_{WHO}) + (1 - P_{WHO}) * R_{WHO\ negative}}{(1 - P_{WHO} \times PR_{IADPSG\_WHO}) + (P_{WHO} * PR_{IADPSG\_WHO} * RR_{IADPSG})}$$

where,

PR_{IADPSG_WHO} = ratio for prevalence increase of GDM with IADPSG criteria compared to 1999 WHO Criteria

RR_{IADPSG} = relative risk for the IADPSG criteria
RR_{WHO} = relative risk for the 1999 WHO criteria

These estimated baseline risks are presented in Table 1 and are close to the incidences of these outcomes observed in untreated women evaluated in the same systematic review.[5]

GDM treatment benefits (Table 1), expressed as lower relative risks, were estimated using data from a separate systematic review.[8]

Sensitivity analysis

To check the robustness of the results, three sensitivity analyses were performed, evaluating different settings:

1) As GDM prevalence varies worldwide, we evaluated the impact of screening strategies based on different prevalence estimates. Thus, alternative models, with prevalence ranging from 5% to 15% according to the 1999 WHO criteria, were performed.
2) Due to the uncertainty regarding the increase in GDM prevalence with the IADPSG criteria, we performed alternative models assuming increases of 25%, 75% and 100% when compared to the 1999 WHO criteria.
3) Given the large size and multi-country, multi-ethnic, population-based nature of the HAPO cohort, we additionally evaluated results from the model starting with the prevalence and baseline risk found in the HAPO cohort population.[4]

Statistical Analysis

We performed Bayesian Monte-Carlo simulations.[16] For each outcome and strategy, the model performed 1.000.000 simulations. We used beta distributions for proportions; and risk and prevalence ratios were converted to natural logarithms and modeled assuming normal distributions. Detailed

information about parameters values, upper and lower limits, and distributions are available in Supplementary Tables 1 and 2.

Results are presented as absolute risk (incidence) reduction and number needed to screen (NNS), with 95% credible (highest probability density) intervals[17] for each outcome. The NNS was computed as the inverse of the absolute risk reduction obtained with each strategy. A 95% credible interval is the most narrow interval that covers 95% of the simulation results.[18,19] Data analysis was performed using the R version 2.11.1 software, package boa.[20] Full syntax of the model is presented in the Appendix 1.

RESULTS

The base case results are presented in Table 2. The expected rates of events when no screening is done are 9.48% (95%CI 8.98% – 9.98%) for having an LGA neonate and 4.81% (95%CI 2.96% – 6.81%) for preeclampsia.

When compared to these rates, universal screening based on the 1999 WHO criteria reduced the incidence of LGA neonates by 0.53% (95% CI 0.37% - 0.74%; $p<0.001$) and in preeclampsia by 0.27% (0.10% - 0.45%; $p<0.001$). The corresponding NNSs to prevent one outcome were 189 and 376, respectively. Similar comparisons with regard to screening based on the IADPSG criteria showed absolute risk reductions of 0.85% (0.54% – 1.29%; $p<0.001$) and 0.39% (0.15% – 0.65%; $p<0.001$), respectively, the corresponding NNSs to prevent one outcome being 117 and 257. Since treatment of GDM was not found to reduce caesarean section rates significantly in the randomized clinical trials reviewed, results obtained from simulations, in consequence, indicate no effect of screening for this outcome.

Table 3 presents information on the quality of the evidence according to GRADE. We classified the quality of the evidence as very low for all outcomes, especially due to indirect evidence, as the impact of screening was assessed only by simulation. Evidence is less strong for the IADPSG

criteria because of high heterogeneity in its associations with outcomes.[5] It is stronger for the outcome of having an LGA neonate, due to the generally larger number of events observed in trials evaluating treatment and cohort studies used to evaluate screening.[5,8]

When compared, treatment based on the IADPSG criteria produced a greater reduction in incidence than that based on the 1999 WHO criteria in 99.97% of the simulations done for LGA neonates, in 99.93% of those for preeclampsia and in 91.07% of those for caesarean section. The adoption of the IADPSG criteria instead of the 1999 WHO criteria would reduce the incidence of LGA neonates by 0.32% (0.09% – 0.63%; $p<0.001$) and of preeclampsia by 0.12% (0.01% – 0.25; $p=0.007$). However, given the small difference in incidence reduction, the NNSs to obtain these additional benefits are large, 309 and 808 for LGA and preeclampsia, respectively. The quality of the evidence for the IADPSG criteria screening strategy being superior to that of the 1999 WHO criteria is also very low (Table 4)

Sensitivity analyses applying the same model to the prevalence and baseline risk found in the HAPO study setting showed similar absolute risk reductions and NNSs for all comparisons (Table 2).

Additional sensitivity analyses were done by altering the prevalence of GDM found with the 1999 WHO criteria. As seen in Figure 1 and in Supplementary Table 3, the NNS decreases as the prevalence of GDM increases. In settings having a low GDM prevalence (for example, 5% according to the 1999 WHO criteria), reductions in incidence are small and NNSs are large for both criteria: for the 1999 WHO criteria, 0.26% (NNS = 378) for LGA neonates and 0.13% (NNS = 753) for preeclampsia; for the IADPSG criteria, 0.44% (NNS = 229) and 0.20% (NNS = 505), respectively. However, in settings of high prevalence (15% by 1999 WHO criteria), incidence reductions of LGA neonates and preeclampsia for the WHO criteria were 0.79% (NNS = 126) and 0.40% (NNS = 251); and for the IADPSG criteria, 1.25% (NNS = 80) and 0.57% (NNS = 174).

Finally, Table 3 and Supplementary Table 3 also show that the impact of the IADPSG criteria is greater when the increase in the prevalence of GDM with these criteria is greater. Assuming a prevalence of 10% according to the 1999 WHO criteria, and prevalence increases of 25%, 50%, 75% and 100% with the adoption of the IADPSG criteria, we observed incidence reductions of 0.72% (NNS=139), 0.85% (NNS=117), 0.98% (NNS=102) and 1.10% (NNS=91) of having an LGA neonate; and of 0.33% (NNS=139), 0.39% (NNS=257), 0.45% (NNS=224) and 0.50% (NNS=199) for preeclampsia, respectively.

DISCUSSION

This is the first study published assessing the impact of screening using the new IADPSG criteria in comparison to the 1999 WHO criteria. Our results show that screening with subsequent treatment of gestational diabetes significantly reduces the incidence of having an LGA neonate and preeclampsia. When based on the 1999 WHO criteria, incidence reduction was 0.53% (NNS = 189) for having an LGA neonate and 0.27% (NNS = 376) for preeclampsia. When based on the IADPSG criteria, incidence reduction of having an LGA neonate was 0.85% (NNS = 117) and of preeclampsia, 0.39% (NNS = 257). Given the greater number of cases detected with screening based on the IADPSG criteria, its implementation rather than the 1999 WHO criteria would reduce the incidence of LGA neonates by 0.32% (NNS = 309) and of preeclampsia by 0.12% (NNS = 808). The quality of evidence that universal screening for GDM prevents these outcomes is very low. No significant effect on caesarean section was observed with any criteria, given that evidence of moderate quality shows that GDM treatment does not produce a clinically significant reduction in this outcome.[8]

Modeling outcomes using estimates of GDM prevalence and baseline risk for outcomes from the HAPO study population did not materially change this result.

Strong points of our study merit mention. This simulation study uses data from recent systematic reviews, the parameters used are objective and derived from the literature, and the process

of simulation is transparent, with the code published as an appendix. We performed sensitivity analysis considering settings, including that of the HAPO study population, with different prevalences of GDM. The quality of the evidence for screening was evaluated objectively according to GRADE.

Our study also has limitations. Being a simulation study, the evidence generated is indirect. Even so, it provides useful information in settings of similar baseline risk and GDM prevalence, given that randomized trials are not available. Further, the parameters available for our simulations are imperfect. First, prediction of outcomes is limited by the heterogeneous results available for IADPSG criteria.[5] Second, the increase in the prevalence of GDM using IADPSG criteria varies substantially in the literature, with some studies describing an increase of only 25%[13,21] and others an increase of more than 100%[14,22] when compared to the 1999 WHO criteria. For the main model, we assumed a base-case of 50%, near to that found in the HAPO study. This assumption may be considered conservative as we would expect a greater reduction in incidence of outcomes when screening and treatment are undertaken in the setting of a greater prevalence of GDM. This was, in fact, demonstrated in our sensitivity analyses. Third, prediction of treatment effects is also uncertain, especially for the IADPSG criteria, which have never been applied in randomized controlled trials of GDM treatment. Thus, we assumed treatment effects (relative risks) to be equal for both criteria.

Yet, our results are useful for policy making as they provide the objective information needed for screening program planning and implementation. Our simulation of the impact of screening strategies in settings having different GDM prevalence was performed to permit assessment of the benefit in different scenarios (Supplementary Table 3). Additionally, we provide the code of our simulation for those who want to perform estimations for their own setting (Appendix 1)

Further research is needed. We could not adequately assess the impact of screening on other important outcomes such as perinatal mortality, shoulder dystocia and intensive care unit admission

because of insufficient information to reliably quantify the impact of screening; however, it is likely that GDM screening would also have a positive effect on these outcomes. Additionally, positive screenees, if advised of their high future risk of diabetes, may adopt healthy habits, the benefits of which may also be attibuted to GDM screening.

Finally, we only assessed the impact of screening strategies based on universal application of the 1999 WHO and the IADPSG criteria. Other screening strategies can be considered, such as a two step approach or selective screening based on risk factors.[23–26]

Although not evaluated, costs are important for screening implementation. A cost-utility analysis found that screening based on the IADPSG criteria was not cost-effective unless long term maternal benefits were also considered.[27]Another recent cost-utility analysis compared this new screening strategy with universal screening according to current American Congress of Obstetricians and Gynecologist guideline (1h glucose challenge test followed by a 3-hour OGTT) finding that the screening strategy based on the IADPSG criteria may be cost-effective for high resources settings ($61,503/QALY), but probably is too costly for most countries.[28]

When evaluating screening options, it is also important to consider the negative aspects related to labeling/treating assymptomatic women. Unfortunately, little has been published in this regard with respect to GDM. However, the diagnosis of GDM may have a negative impact psychologically and in women´s perception of their own health. [29–31]

In conclusion, universal screening followed by specific GDM treatment has only a modest impact on pregnancy outcomes. Although the impact based on the IADPSG criteria is slightly larger than that based on the 1999 WHO criteria, issues of cost-effectiveness and availability of resources must also be considered in decisions related to the selection of criteria for local implementation.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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M.F. wrote the protocol, developed the statistical model and wrote the manuscript. I.P. reviewed the statistical model and wrote the code. B.B.D., S.C. and G.R. contributed to discussion and reviewed the manuscript. M.I.S. participated in all the aspects of the project and was the overall supervisor.

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Table 1 – Parameters used in the main model

Parameter	Base Case	Lower Limit	Upper Limit
GDM prevalence according to 1999 WHO criteria	10%	-	-
GDM prevalence according to IADPSG criteria (1999 WHO x 1.5)	15%	13.0%	17.3%
Probability of woman with GDM receiving treatment	90%	80%	97%
Baseline (without treatment) risk of a given outcome in 1999 WHO criteria negative women			
LGA neonate	9%	8.5%	9.5%
Preeclampsia	4.5%	2.9%	6.5%
Caesarean section	18.5%	10%	29%
Relative risk of outcome for women meeting 1999 WHO criteria			
LGA neonate	1.53	1.39	1.69
Preeclampsia	1.69	1.31	2.18
Caesarean section	1.37	1.24	1.51
Baseline (without treatment) risk of given outcome in IADPSG criteria negative women*			
LGA neonate	8.75%	8.18%	9,31%
Preeclampsia	4.42%	2.81%	6.37%
Caesarean section	18.5%	10%	29.1%
Relative risk of outcome for women meeting IADPSG criteria			
LGA neonate	1.73	1.27	2.35
Preeclampsia	1.71	1.37	2.12
Caesarean section	1.23	1.01	1.51
GDM treatment benefit (Relative risk)			
LGA neonate	0.57	0.47	0.71
Preeclampsia	0.61	0.46	0.81
Caesarean section	0.90	0.78	1.05

GDM – Gestational diabetes mellitus; LGA – Large for gestational age; WHO– World Health Organization; IADPSG – International Association of Diabetes in Pregnancy Study Groups

* see text for calculations; limits estimated by simulation.

Table 2 – Impact (absolute risk reduction and number needed to screen) of screening strategies, compared to no screening, for having a large for gestational age (LGA) neonate, preeclampsia and caesarean section.

	No screening	**1999 WHO criteria based screening**			**IADPSG criteria based screening**		
	Incidence (%) (95%CI)	Incidence (%) (95%CI)	ARR (%) (95%CI)	NNS (95%CI)	Incidence (%) (95%CI)	ARR (%) (95%CI)	NNS (95%CI)
Main model							
LGA Neonate	9.48% (8.98% – 9.98%)	8.95% (8.43% –9.41%)	0.53% (0.37% - 0.74%)	189 (134 – 268)	8.63% (7.99% – 9.16%)	0.85% (0.54% -1.29%)	117 (77 – 185)
Preeclampsia	4.81% (2.96% – 6.81%)	4.54% (2.79% – 6.44%)	0.27% (0.10% -0.45%)	376 (223 – 1010)	4.42% (2.70% – 6.27%)	0.39% (0.15% -0.65%)	257 (154 – 679)
Caesarean Section	19.18% (9.83% – 29.15%)	18.93% (9.74% – 28.85%)	0.25% (-0.12% – 0.60%)	399 (165 - -848)	18.84% (9.68% – 28.71%)	0.34% (-0.16% – 0.83%)	296 (120 - -622)
Model applied to the HAPO setting							
LGA Neonate	9.57%	8.97% (8.74% - 9.14%)	0.60% (0.43% – 0.83%)	167 (120 – 231)	8.57% (8.19% - 8.85%)	1.00% (0.72% – 1.38%)	100 (77 – 185)
Preeclampsia	5.22%	4.92% (4.79% - 5.06%)	0.30% (0.16% – 0.43%)	331 (232 –633)	4,71% (4,49% - 4,95%)	0.51% (0.27% – 0.73%)	196 (137 – 374)
Caesarean Section	18%	17.74% (17.4% - 18.11%)	0.26% (-0.11% – 0.60%)	383 (167 - -944)	17.63% (17.15% - 18.15%)	0.37% (-0.15% – 0.85%)	272 (118 - -669)

CI: Credible interval; ARR – Absolute risk reduction; NNS – Number needed to screen; HAPO – Hyperglycemia and Adverse Pregnancy Outcomes Study; WHO – World Health Organization; IADPSG – International Association of Diabetes in Pregnancy Study Groups; LGA – Large for gestational age

Table 3 - GRADE evaluation of screening for gestational diabetes (GDM) based on the universal application of the 1999 WHO and the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria

Screening for GDM according to the 1999 WHO and to the IADPSG criteria compared to no screening strategy in pregnancy
Population: pregnant women from general population
Intervention: 75g oral glucose tolerance test, with specific treatment for women diagnosed with GDM according to the 1999 WHO or the IADPSG criteria
Comparison: no screening strategy
Outcome: adverse perinatal and maternal outcomes

Comparison	Outcome	ARR (%) (95%CI)	NNS (95%CI)	Quality assessment	Quality	Importance
Screening strategy based on the 1999 WHO criteria versus no screening strategy	LGA neonate	0.53% (0.37% - 0.74%)	189 (134 – 268)	Cohort-based simulated population. No serious limitations, inconsistency or imprecision; very serious indirectness (cohort simulation)	Very Low	Important
	Preeclampsia	0.27% (0.10% -0.45%)	376 (223 – 1010)	Cohort-based simulated population. No serious limitations or inconsistency; very serious indirectness (cohort simulation); serious imprecision (small number of outcomes for preeclampsia in randomized clinical trials)	Very Low	Critical
	Caesarean section	0.25% (-0.12% – 0.60%)	399 (165 – -848)	Cohort-based simulated population. Serious limitations (unblinded trials or selective blinding for control group in the evaluation of treatment efficacy); no serious inconsistency or imprecision; very serious indirectness (cohort simulation)	Very Low	Critical
Screening strategy based on the IDPSGA criteria versus no screening strategy	LGA neonate	0.85% (0.54% -1.29%)	117 (77 – 185)	Cohort-based simulated population. No serious limitations or imprecision; serious inconsistency (heterogeneity in the predictive value for IADPSG criteria); very serious indirectness (cohort simulation)	Very Low	Important
	Preeclampsia	0.39% (0.15% -0.65%)	257 (154 – 679)	Cohort-based simulated population. No serious limitations; serious inconsistency (heterogeneity in the predictive value for IADPSG criteria); very serious indirectness (cohort simulation); serious imprecision (small number of outcomes for preeclampsia in randomized clinical trials)	Very Low	Critical
	Caesarean section	0.34% (-0.16% – 0.83%)	296 (120 – -622)	Cohort-based simulated population. Serious limitations (unblinded trials or selective blinding for control group in the evaluation of treatment efficacy); serious inconsistency (heterogeneity in the predictive value for IADPSG criteria); very serious indirectness (cohort simulation); no serious imprecision	Very Low	Critical

ARR – Absolute risk reduction; NNS – Number needed to screen; CI – Credible interval; LGA – Large for gestational age; WHO – World Health Organization; IADPSG – International Association of Diabetes in Pregnancy Study Groups

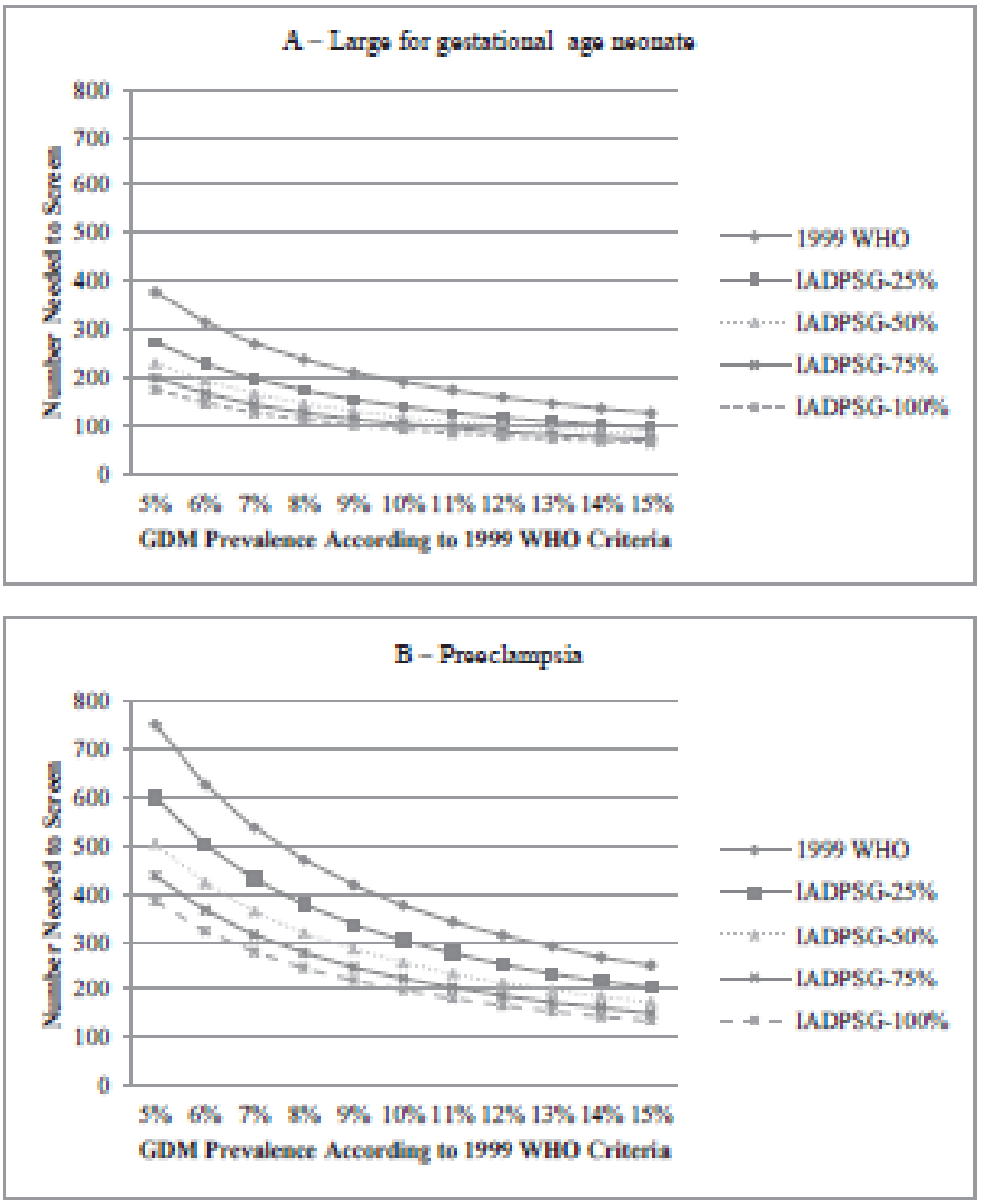
Table 4 - GRADE evaluation of screening for gestational diabetes mellitus (GDM) based on the universal application of the IADPSG criteria instead of the 1999 WHO criteria.

Screening for GDM according to IADPSG criteria compared to 1999 WHO criteria
Population: pregnant women from general population
Intervention: 75g oral glucose tolerance test, with specific treatment for women diagnosed with GDM according to IADPSG criteria
Comparison: 75g oral glucose tolerance test, with specific treatment for women diagnosed with GDM according to 1999 WHO criteria
Outcome: adverse perinatal and maternal outcomes

Outcome	**ARR (%) (95%CI)**	**NNS (95%CI)**	**Quality assessment**	**Quality**	**Importance**
LGA neonate	0.32% (0.09% - 0.63%)	309 (159 – 1053)	Cohort-based simulated population. No serious limitations or imprecision; serious inconsistency (heterogeneity in the predictive value for IADPSG criteria); very serious indirectness (cohort simulation)	Very Low	Important
Preeclampsia	0.12% (0.01% - 0.25%)	808 (395 - 9486)	Cohort-based simulated population. No serious limitations; serious inconsistency (heterogeneity in the predictive value for IADPSG criteria); very serious indirectness (cohort simulation); serious imprecision (small number of outcomes for preeclampsia in randomized clinical trials)	Very Low	Critical
Caesarean section	0.09% (-0.05% - 0.26%)	1141 (389 - -2075)	Cohort-based simulated population. Serious limitations (unblinded trials or selective blinding for control group in the evaluation of treatment efficacy); serious inconsistency (heterogeneity in the predictive value for IADPSG criteria); very serious indirectness (cohort simulation); no serious imprecision	Very Low	Critical

ARR – Absolute risk reduction; NNS – Number needed to screen; LGA – Large for gestational age; WHO – World Health Organization; IADPSG – International Association of Diabetes in Pregnancy Study Groups

Figure 1. Sensitivity analysis: Number needed to screen in settings of varying prevalence of gestational diabetes mellitus (GDM) and when assuming different increases in the prevalence with use of the IADPSG criteria instead of the 1999 WHO criteria.



1999 WHO – screening strategy based on the 1999 World Health Organization criteria; IADPSG – screening strategy based on the International Association of Diabetes in Pregnancy Study Groups criteria, with 25%, 50%, 75% and 100% of increase in the prevalence compared to the 1999 WHO criteria

Supplementary Table 1: Variables in the model simulation

Variable	Description
PWHO	Prevalence of GDM according to the 1999 WHO criteria
LGA_IWHO_negative	Baseline risk of LGA for women without GDM based on the 1999 WHO criteria
PE_IWHO_negative	Baseline risk of preeclampsia for women without GDM based on the 1999 WHO criteria
CS_IWHO_negative	Baseline risk of caesarean section for women without GDM based on the 1999 WHO criteria
Ptreatment	Probability of a woman screened as positive for GDM receive adequate treatment
logRPiadpsg	Natural logarithm of the prevalence ratio for the prevalence increase of GDM with the IADPSG criteria instead of the 1999 WHO criteria
LGA_logRRWHO	Natural logarithm of the risk ratio for the incidence of LGA neonates for woman with GDM based on the 1999 WHO criteria
LGA_logRRiadpsg	Natural logarithm of the risk ratio for the incidence of LGA neonates for woman with GDM based on the IADPSG criteria
PE_logRRWHO	Natural logarithm of the risk ratio for the incidence of preeclampsia for woman with GDM based on the 1999 WHO criteria
PE_logRRiadpsg	Natural logarithm of the risk ratio for the incidence of preeclampsia for woman with GDM based on the IADPSG criteria
CS_logRRWHO	Natural logarithm of the risk ratio for the incidence of caesarean section for woman with GDM based on the 1999 WHO criteria
CS_logRRiadpsg	Natural logarithm of the risk ratio for the incidence of caesarian section for woman with GDM based on the IADPSG criteria
LGA_logRRtreatment	Natural logarithm of the risk ratio for the incidence of LGA neonates for woman with GDM that received adequate treatment
PE_logRRtreatment	Natural logarithm of the risk ratio for the incidence of preeclampsia for woman with GDM that received adequate treatment
CS_logRRtreatment	Natural logarithm of the risk ratio for the incidence of caesarean section for woman with GDM that received adequate treatment
PWHO_HAPO	Prevalence of GDM according to the 1999 WHO criteria in the HAPO study
Piadpsg_HAPO	Prevalence of GDM according to the IADPSG criteria in the HAPO study
LGA_IWHOpos_HAPO	Incidence of LGA neonates for woman with GDM based on the 1999 WHO criteria in the HAPO study
PE_IWHOpos_HAPO	Incidence of LGA neonates for woman with GDM based on the 1999 WHO criteria in the HAPO study
CS_IWHOpos_HAPO	Incidence of caesarean section for woman with GDM based on the 1999 WHO criteria in the HAPO study
LGA_Iiadpsgpos_HAPO	Incidence of LGA neonates for woman with GDM based on the 1999 WHO criteria in the HAPO study
PE_Iiadpsgpos_HAPO	Incidence of preeclampsia for woman with GDM based on the IADPSG criteria in the HAPO study
CS_ Iiadpsgpos_HAPO	Incidence of caesarean section for woman with GDM based on the IADPSG criteria in the HAPO study

GDM – Gestational diabetes mellitus; WHO – World Health Organization; IADPSG – International Association of Diabetes in Pregnancy Study Groups; LGA – Large for gestational age; HAPO – Hyperglycemia and Adverse Pregnancy Outcomes Study;

Supplementary Table 2: Parameters used in the model simulation

Variable*	Mean	Standard Deviation	Lower limit	Upper limit	Distribution
PWHO	0.1	-	-	-	Constant
LGA_IWHO_negative	0.09	-	0.085	0.095	Beta
PE_IWHO_negative	0,045	-	0.029	0.065	Beta
CS_IWHO_negative	0,185	-	0.10	0.29	Beta
Ptreatment	0,90	-	0.80	0.97	Beta
logRPiadpsg	0.4055	0.0730	-	-	Normal
LGA_logRRWHO	0.4256	0.0494	-	-	Normal
LGA_logRRiadpsg	0.5503	0.1558	-	-	Normal
PE_logRRWHO	0.5260	0.1288	-	-	Normal
PE_logRRiadpsg	0.5374	0.1108	-	-	Normal
CS_logRRWHO	0.3144	0.0508	-	-	Normal
CS_logRRiadpsg	0.2086	0.1035	-	-	Normal
LGA_logRRtreatment	-0.5554	0.1059			Normal
PE_logRRtreatment	-0.4903	0.1413	-	-	Normal
CS_logRRtreatment	-0.1100	0.0797	-	-	Normal
PWHO_HAPO	0.114	-	-	-	Constant
Piadpsg_HAPO	0.161	-	-	-	Constant
LGA_IWHOpos_HAPO	0.137	-	-	-	Constant
PE_IWHOpos_HAPO	0.076	-	-	-	Constant
CS_IWHOpos_HAPO	0.244	-	-	-	Constant
LGA_Iiadpsgpos_HAPO	0.162	-	-	-	Constant
PE_Iiadpsgpos_HAPO	0.091	-	-	-	Constant
CS_ Iiadpsgpos_HAPO	0.244	-	-	-	Constant

Footnote:

*Variable names are described in supplementary table 1

Appendix 1: Simulation cohort: syntax of the model

```
#############################################################################################################
# Impact of Gestational Diabetes Mellitus Screening Strategies on Perinatal Outcomes: a Simulation Study
# Coded by: Isaias Prestes; reviewed by Maicon Falavigna
# Performed on R version 2.11.1
# Packages required: hdrcde, boa
# Date: 01/06/12
#############################################################################################################


# Settings
n <- 1000000 ;
alfa <- 0.05

# The Beta distribution with parameters shape1 = a and shape2 = b has density
#
# G(a+b)/(G(a)G(b))x^(a-1)(1-x)^(b-1)
#
# for a > 0, b > 0 and 0 = x = 1 where the boundary values at x=0 or x=1 are defined as by continuity (as limits).
# The mean is a/(a+b) and the variance is ab/((a+b)^2 (a+b+1)).

# Given a and b, return a array with mean, variance, deviation, lower endpoint and upper endpoint of the 100(1-alfa)% confidence interval for
Beta distribution.
beta.parametros <- function(a, b, alfa, digits = 5) {
       media <- a / (a+b)
       variancia <- (a * b)/ ( (a+b)^2 * (a+b+1) )
       liminf <- qbeta(alfa/2, a, b)
       limsup <- qbeta(1 - alfa/2, a, b)
       return( round( c("Mean"=media,"Var"=variancia,"SD"=variancia^.5, "LL"=liminf, "UL"=limsup) , digits=5) )
}
# Example :
beta.parametros(3, 6, alfa)

# Set RNG seed
set.seed(37589411)

# Values for PWHO
# PWHO <- seq(0.05,0.15,0.01)
PWHO <- 0.05

# Simulated parameters values

# LGA Birth (LGA)
```

```
LGA_Iwho_negative <- rbeta(n, 1.5*900, 1.5*9100 ) ; c <- 1.5; beta.parametros(c*900, 9100*c, alfa)
LGA_logRRwho <- rnorm(n, 0.4256, 0.0494) ;          # Distribution for log(RR)
LGA_Ptreatment <- rbeta(n, 40.5,  4.5 ) ; c <- 4.5; beta.parametros(9*c, 1*c, alfa) # approximated solution
LGA_logRPiadpsg <- rnorm(n, 0.4055, 0.0730) ;              # Distribution for log(RP)
LGA_logRRtreatment <- rnorm(n, -0.6095, 0.1245) ;   # Distribution for log(RR)
LGA_logRRiadpsg <- rnorm(n, 0.5503, 0.1558) ;              # Distribution for log(RR)

# Preeclampsia (PE)
PE_Iwho_negative <- rbeta(n, 22.5, 477.5 ) ; c <- 0.5; beta.parametros(c*45, c*955, alfa)
PE_logRRwho <- rnorm(n, 0.5260, 0.1288) ;           # Distribution for log(RR)
PE_Ptreatment <- rbeta(n, 40.5,  4.5 ) ; c <- 4.5; beta.parametros(9*c, 1*c, alfa) # approximated solution
PE_logRPiadpsg <- rnorm(n, 0.4055, 0.0730) ;        # Distribution for log(RP)
PE_logRRtreatment <- rnorm(n, -0.4903, 0.1413) ;    # Distribution for log(RR)
PE_logRRiadpsg <- rnorm(n, 0.5374, 0.1108) ;        # Distribution for log(RR)

# Caesarean section (CS)
CS_Iwho_negative <- rbeta(n, 11.7475, 51.7525 ) ; beta.parametros(11.7475, 51.7525, alfa)
CS_logRRwho <- rnorm(n, 0.3144, 0.0508) ;           # Distribution for log(RR)
CS_Ptreatment <- rbeta(n, 40.5,  4.5 ) ; c <- 4.5; beta.parametros(9*c, 1*c, alfa) # approximated solution
CS_logRPiadpsg <- rnorm(n, 0.4055, 0.0730) ;        # Distribution for log(RP)
CS_logRRtreatment <- rnorm(n, -0.1100, 0.0797) ;           # Distribution for log(RR)
CS_logRRiadpsg <- rnorm(n, 0.2086, 0.1035) ;        # Distribution for log(RR)

# Set simulated block
set.idiaf <- function( PWHO, Iwho_negative, logRRwho, Ptreatment, logRRtreatment, logRPiadpsg, logRRiadpsg) {
       IDIAF <- ( ( PWHO * Iwho_negative * exp(logRRwho) ) ) + ( ( 1 - PWHO ) * Iwho_negative ) / ( (1 - ( PWHO * exp(logRPiadpsg) ) ) + (
exp(logRRiadpsg) * PWHO * exp(logRPiadpsg) ) )
       return(IDIAF)
}

# Functions for model simulation
simula.nao.rastrear <- function ( n , PWHO, Iwho_negative, logRRwho, Ptreatment, logRRtreatment, logRPiadpsg, logRRiadpsg) {
       Iwho_positive <- Iwho_negative * exp(logRRwho) # Iwho_positive = Iwho_negative * RRwho

       ans <- (
                        ( PWHO * Iwho_positive ) + ( ( 1 - PWHO ) * Iwho_negative )
                )

       return(ans)
}

simula.who <- function ( n , PWHO, Iwho_negative, logRRwho, Ptreatment, logRRtreatment, logRPiadpsg, logRRiadpsg) {
       Iwho_positive <- Iwho_negative * exp(logRRwho)

       ans <- (
                        ( ( 1 - PWHO ) * Iwho_negative ) +
```

```
                        ( PWHO * ( 1 - Ptreatment ) * Iwho_positive ) +
                        ( PWHO * Ptreatment * exp(logRRtreatment) * Iwho_positive )
                )

        return(ans)
}

simula.iadpsg <- function ( n , PWHO, Iwho_negative, logRRwho, Ptreatment, logRRtreatment, logRPiadpsg, logRRiadpsg) {

        Piadpsg <- PWHO * exp(logRPiadpsg)   # Piadpsg = Pwho * PRiadpsg

        Iiadpsg_negative <- ( ( PWHO * Iwho_negative * exp(logRRwho) ) +
                                        ( ( 1 - PWHO) * Iwho_negative ) ) / ( ( ( 1 - (PWHO * exp(logRPiadpsg) ) ) )  +
                                        ( PWHO * exp(logRPiadpsg) * exp(logRRiadpsg) ) )

        Iiadpsg_positive <- Iiadpsg_negative * exp(logRRiadpsg)

        ans <- (
                        ( ( 1 - Piadpsg ) * Iiadpsg_negative ) +
                        ( Piadpsg * Iiadpsg_positive * Ptreatment * exp(logRRtreatment) ) +
                        ( Piadpsg * Iiadpsg_positive * ( 1 - Ptreatment ) )
                )

        return(ans)
}

# Looping PWHO values
datasummary <- array(,10)
datasummary.diff <- array(,10)
datasummary.table.diff <- array(,3)

names(datasummary) <- c("PWHO", "Strategy", "Min.",    "1st Qu.", "Median",  "Mean",    "3rd Qu.", "Max.")
names(datasummary.diff) <- c("PWHO", "Strategy", "Min.",    "1st Qu.", "Median",  "Mean",    "3rd Qu.", "Max.")

for ( i in PWHO ) {
        arrayPWHO <- rep(i, n)
        # Compute values for each screening strategies
        resultados.IADPSG.LGA <- simula.iadpsg(  n , arrayPWHO, LGA_Iwho_negative, LGA_logRRwho, LGA_Ptreatment, LGA_logRRtreatment,
LGA_logRPiadpsg, LGA_logRRiadpsg)
        resultados.IADPSG.PE <- simula.iadpsg(  n , arrayPWHO, PE_Iwho_negative, PE_logRRwho, PE_Ptreatment, PE_logRRtreatment, PE_logRPiadpsg,
PE_logRRiadpsg)
        resultados.IADPSG.CS <- simula.iadpsg(  n , arrayPWHO, CS_Iwho_negative, CS_logRRwho, CS_Ptreatment, CS_logRRtreatment, CS_logRPiadpsg,
CS_logRRiadpsg)

        resultados.NR.LGA <- simula.nao.rastrear(  n , arrayPWHO, LGA_Iwho_negative, LGA_logRRwho, LGA_Ptreatment, LGA_logRRtreatment,
LGA_logRPiadpsg, LGA_logRRiadpsg)
```

```
	resultados.NR.PE <- simula.nao.rastrear(  n , arrayPWHO, PE_Iwho_negative, PE_logRRwho, PE_Ptreatment, PE_logRRtreatment, PE_logRPiadpsg,
PE_logRRiadpsg)
	resultados.NR.CS <- simula.nao.rastrear(  n , arrayPWHO, CS_Iwho_negative, CS_logRRwho, CS_Ptreatment, CS_logRRtreatment, CS_logRPiadpsg,
CS_logRRiadpsg)

	resultados.WHO.LGA <- simula.who(  n , arrayPWHO, LGA_Iwho_negative, LGA_logRRwho, LGA_Ptreatment, LGA_logRRtreatment, LGA_logRPiadpsg,
LGA_logRRiadpsg)
	resultados.WHO.PE <- simula.who(  n , arrayPWHO, PE_Iwho_negative, PE_logRRwho, PE_Ptreatment, PE_logRRtreatment, PE_logRPiadpsg,
PE_logRRiadpsg)
	resultados.WHO.CS <- simula.who(  n , arrayPWHO, CS_Iwho_negative, CS_logRRwho, CS_Ptreatment, CS_logRRtreatment, CS_logRPiadpsg,
CS_logRRiadpsg)

	resultado.final <- data.frame(
		"PWHO" = arrayPWHO,
		"NR.LGA" = resultados.NR.LGA,
		"NR.PE" = resultados.NR.PE,
		"NR.CS" = resultados.NR.CS,
		"WHO.LGA" = resultados.WHO.LGA,
		"WHO.PE" = resultados.WHO.PE,
		"WHO.CS" = resultados.WHO.CS,
		"IADPSG.LGA" = resultados.IADPSG.LGA,
		"IADPSG.PE" = resultados.IADPSG.PE,
		"IADPSG.CS" = resultados.IADPSG.CS
		)

	write.csv2( resultado.final , paste("table_data_PWHO_", i,".csv", sep="") )

	# Compute differences
	Delta.NR.WHO.LGA <- resultados.NR.LGA  -  resultados.WHO.LGA
	Delta.NR.IADPSG.LGA <- resultados.NR.LGA  -  resultados.IADPSG.LGA
	Delta.WHO.IADPSG.LGA <- resultados.WHO.LGA - resultados.IADPSG.LGA

	Delta.NR.WHO.PE <- resultados.NR.PE  -  resultados.WHO.PE
	Delta.NR.IADPSG.PE <- resultados.NR.PE  -  resultados.IADPSG.PE
	Delta.WHO.IADPSG.PE <- resultados.WHO.PE - resultados.IADPSG.PE

	Delta.NR.WHO.CS <- resultados.NR.CS  -  resultados.WHO.CS
	Delta.NR.IADPSG.CS <- resultados.NR.CS  -  resultados.IADPSG.CS
	Delta.WHO.IADPSG.CS <- resultados.WHO.CS - resultados.IADPSG.CS

	# Compute p-values empirical # Pr { standart strategy > alternative strategy }
	comptype <-
c("NR.WHO.LGA","NR.IADPSG.LGA","WHO.IADPSG.LGA","NR.WHO.PE","NR.IADPSG.PE","WHO.IADPSG.PE","NR.WHO.CS","NR.IADPSG.CS","WHO.IADPSG.CS")
	resultados.pvalue <- array(,0)

	for (i in comptype) {
```

```
		ans <- c(i, eval(parse(text=paste("sum( ifelse(Delta.",i ," < 0 , 1, 0) ) / n",sep=""))) )
		resultados.pvalue <- rbind(resultados.pvalue, ans)
		print( ans )
	}

	write.csv2( resultados.pvalue , paste("Summary_pvalues.csv", sep=""))

	# NNS for screening strategies
	NNS.Delta.NR.WHO.LGA <- 1 / Delta.NR.WHO.LGA
	NNS.Delta.NR.IADPSG.LGA <- 1 / Delta.NR.IADPSG.LGA
	NNS.Delta.WHO.IADPSG.LGA <- 1 / Delta.WHO.IADPSG.LGA

	NNS.Delta.NR.WHO.PE <- 1 / Delta.NR.WHO.PE
	NNS.Delta.NR.IADPSG.PE <- 1 / Delta.NR.IADPSG.PE
	NNS.Delta.WHO.IADPSG.PE <- 1 / Delta.WHO.IADPSG.PE

	NNS.Delta.NR.WHO.CS <- 1 / Delta.NR.WHO.CS
	NNS.Delta.NR.IADPSG.CS <- 1 / Delta.NR.IADPSG.CS
	NNS.Delta.WHO.IADPSG.CS <- 1 / Delta.WHO.IADPSG.CS

	# Compute binary variables for proportions
	Bin.Delta.NR.WHO.LGA <- ifelse(Delta.NR.WHO.LGA > 0, 1, 0)
	Bin.Delta.NR.IADPSG.LGA <- ifelse(Delta.NR.IADPSG.LGA > 0, 1, 0)
	Bin.Delta.WHO.IADPSG.LGA <- ifelse(Delta.WHO.IADPSG.LGA > 0, 1, 0)

	Bin.Delta.NR.WHO.PE <- ifelse(Delta.NR.WHO.PE > 0, 1, 0)
	Bin.Delta.NR.IADPSG.PE <- ifelse(Delta.NR.IADPSG.PE > 0, 1, 0)
	Bin.Delta.WHO.IADPSG.PE <- ifelse(Delta.WHO.IADPSG.PE > 0, 1, 0)

	Bin.Delta.NR.WHO.CS <- ifelse(Delta.NR.WHO.CS > 0, 1, 0)
	Bin.Delta.NR.IADPSG.CS <- ifelse(Delta.NR.IADPSG.CS > 0, 1, 0)
	Bin.Delta.WHO.IADPSG.CS <- ifelse(Delta.WHO.IADPSG.CS > 0, 1, 0)

	comptype <-
c("NR.WHO.LGA","NR.IADPSG.LGA","WHO.IADPSG.LGA","NR.WHO.PE","NR.IADPSG.PE","WHO.IADPSG.PE","NR.WHO.CS","NR.IADPSG.CS","WHO.IADPSG.CS")

	for (i in comptype) {
		ans <- eval(parse(text=paste("table(Bin.Delta.",i,")",sep="")))
		print(ans)

		if ( length(ans) < 2 ) ans <- c("0" = 0, ans[1] )
		datasummary.table.diff <- rbind( datasummary.table.diff, as.array(c(i,ans)) )
	}

	# Save data
	datasummary.table.diff <- datasummary.table.diff[ !is.na(datasummary.table.diff[,1]) ,]
```

```
datasummary.table.diff <- data.frame(
       "Comparação" = as.character(datasummary.table.diff[,1]),
       "Freq 0" = as.numeric(as.character(datasummary.table.diff[,2])),
       "Freq 1" = as.numeric(as.character(datasummary.table.diff[,3])),
       "Fr 0" = (100 * (as.numeric(as.character(datasummary.table.diff[,2])) / n )),
       "Fr 1" = (100 * (as.numeric(as.character(datasummary.table.diff[,3])) / n ))
       )

write.csv2( datasummary.table.diff , "Estatísticas_Binarias_Prop_Comp.csv", row.names=FALSE )

resultado.final.diff <- data.frame(
       "PWHO" = arrayPWHO,
       "NR vs WHO - LGA" = Delta.NR.WHO.LGA,
       "NR vs IADPSG - LGA" = Delta.NR.IADPSG.LGA,
       "WHO vs IADPSG - LGA" = Delta.WHO.IADPSG.LGA,

       "NR vs WHO - PE" = Delta.NR.WHO.PE,
       "NR vs IADPSG - PE" = Delta.NR.IADPSG.PE,
       "WHO vs IADPSG - PE" = Delta.WHO.IADPSG.PE,

       "NR vs WHO - CS" = Delta.NR.WHO.CS,
       "NR vs IADPSG - CS" = Delta.NR.IADPSG.CS,
       "WHO vs IADPSG - CS" = Delta.WHO.IADPSG.CS

       )

write.csv2( resultado.final.diff , paste("table_data_Differences_PWHO_", i,".csv", sep=""), row.names=FALSE )

# Compute summary tables
datasummary <- rbind( datasummary, c( i, "NR.LGA", c(summary(resultado.final$"NR.LGA",)) ,
       quantile(resultado.final$"NR.LGA", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
datasummary <- rbind( datasummary, c( i, "NR.PE", c(summary(resultado.final$"NR.PE")) ,
       quantile(resultado.final$"NR.LGA", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
datasummary <- rbind( datasummary, c( i, "NR.CS", c(summary(resultado.final$"NR.CS")) ,
       quantile(resultado.final$"NR.LGA", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )

datasummary <- rbind( datasummary, c( i, "WHO.LGA", c(summary(resultado.final$"WHO.LGA")) ,
       quantile(resultado.final$"WHO.LGA", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
datasummary <- rbind( datasummary, c( i, "WHO.PE", c(summary(resultado.final$"WHO.PE")) ,
       quantile(resultado.final$"WHO.PE", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
datasummary <- rbind( datasummary, c( i, "WHO.CS", c(summary(resultado.final$"WHO.CS")) ,
       quantile(resultado.final$"WHO.CS", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )

datasummary <- rbind( datasummary, c( i, "IADPSG.LGA", c(summary(resultado.final$"IADPSG.LGA")) ,
       quantile(resultado.final$"IADPSG.LGA", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
```

```
        datasummary <- rbind( datasummary, c( i, "IADPSG.PE", c(summary(resultado.final$"IADPSG.PE")) ,
               quantile(resultado.final$"IADPSG.PE", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
        datasummary <- rbind( datasummary, c( i, "IADPSG.CS", c(summary(resultado.final$"IADPSG.CS")) ,
               quantile(resultado.final$"IADPSG.CS", probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )

        # Compute summary tables for differences
        datasummary.diff <- rbind( datasummary.diff, c( i, "NR vs WHO - LGA", c(summary(Delta.NR.WHO.LGA)) ,
               quantile(Delta.NR.WHO.LGA, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
        datasummary.diff <- rbind( datasummary.diff, c( i, "NR vs IADPSG - LGA", c(summary(Delta.NR.IADPSG.LGA)) ,
               quantile(Delta.NR.IADPSG.LGA, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )

        # Compute summary : screening strategies WHO vs IADPSG for LGA
        datasummary.diff <- rbind( datasummary.diff, c( i, "WHO vs IADPSG - LGA", c(summary(Delta.WHO.IADPSG.LGA)) ,
               quantile(Delta.WHO.IADPSG.LGA, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
        datasummary.diff <- rbind( datasummary.diff, c( i, "NR vs WHO - PE", c(summary(Delta.NR.WHO.PE)) ,
               quantile(Delta.NR.WHO.PE, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
        datasummary.diff <- rbind( datasummary.diff, c( i, "NR vs IADPSG - PE", c(summary(Delta.NR.IADPSG.PE)) ,
               quantile(Delta.NR.IADPSG.PE, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )

        # Compute summary : screening strategies WHO vs IADPSG for PE
        datasummary.diff <- rbind( datasummary.diff, c( i, "WHO vs IADPSG - PE", c(summary(Delta.WHO.IADPSG.PE)) ,
               quantile(Delta.WHO.IADPSG.PE, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
        datasummary.diff <- rbind( datasummary.diff, c( i, "NR vs WHO - CS", c(summary(Delta.NR.WHO.CS)) ,
               quantile(Delta.NR.WHO.CS, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
        datasummary.diff <- rbind( datasummary.diff, c( i, "NR vs IADPSG - CS", c(summary(Delta.NR.IADPSG.CS)) ,
               quantile(Delta.NR.IADPSG.CS, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )

        # Compute summary : screening strategies WHO vs IADPSG for CS
        datasummary.diff <- rbind( datasummary.diff, c( i, "WHO vs IADPSG - CS", c(summary(Delta.WHO.IADPSG.CS)) ,
               quantile(Delta.WHO.IADPSG.CS, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
}

# Save summary data
datasummary <- datasummary[ !is.na(datasummary[,1]) ,]
datasummary.diff <- datasummary.diff[ !is.na(datasummary.diff[,1]) ,]

datasummary <- data.frame(datasummary)
names(datasummary) <- c(names(datasummary)[1:(length(names(datasummary))-2)],
paste("Percentil ",round((alfa/2)*100, digits=1),sep=""), paste("Percentil ",round((1-alfa/2)*100, digits=1),sep=""))

datasummary.diff <- data.frame(datasummary.diff)
names(datasummary.diff) <- c(names(datasummary.diff)[1:(length(names(datasummary))-2)],
paste("Percentil ",round((alfa/2)*100, digits=1),sep=""), paste("Percentil ",round((1-alfa/2)*100, digits=1),sep=""))

write.csv2( datasummary , paste("Summary_statistics.csv", sep=""), row.names=FALSE )
write.csv2( datasummary.diff , paste("Summary_statistics_for_differences.csv", sep=""), row.names=FALSE )
```

```
# Summary - distribution - Compute the Highest Posterior Density Interval (HPD)
require(hdrcde)
require(boa)

comptype <- c("NR.LGA","NR.PE","NR.CS","WHO.LGA","WHO.PE","WHO.CS","IADPSG.LGA","IADPSG.PE","IADPSG.CS")

for (i in comptype) {
       print(paste("Computing HPD Interval for ",i,sep=""))

       graphname <- paste("grafico_",i,".png", sep="")
       png(file.path(paste(getwd(),"//saida", sep=""),graphname))
              ans <- hdr.den(resultado.final[,i])
       dev.off()

       # Using boa package
       ans <- boa.hpd(resultado.final[,i], alpha = 0.05)
       write.csv2( ans , paste("HPD ",i,".csv", sep=""))
       print( ans )

}

comptype <-
c("NR.WHO.LGA","NR.IADPSG.LGA","WHO.IADPSG.LGA","NR.WHO.PE","NR.IADPSG.PE","WHO.IADPSG.PE","NR.WHO.CS","NR.IADPSG.CS","WHO.IADPSG.CS")

for (i in comptype) {
       print(paste("Computing HPD Interval for Difference ",i,sep=""))

       graphname <- paste("grafico_IDiff_",i,".png", sep="")
       png(file.path(paste(getwd(),"//saida", sep=""),graphname))
              ans <- eval(parse(text=paste("hdr.den(Delta.",i,")",sep="")))
       dev.off()

       # Using boa package
       ans <- eval(parse(text=paste("boa.hpd(Delta.",i,", alpha = 0.05)",sep="")))
       write.csv2( ans , paste("HPD Diff ",i,".csv", sep=""))
       print( ans )

}

comptype <-
c("NR.WHO.LGA","NR.IADPSG.LGA","WHO.IADPSG.LGA","NR.WHO.PE","NR.IADPSG.PE","WHO.IADPSG.PE","NR.WHO.CS","NR.IADPSG.CS","WHO.IADPSG.CS")

for (i in comptype) {
       print(paste("Computing HPD Interval for NNS",i,sep=""))
```

```
        graphname <- paste("grafico_NNS_Diff_",i,".png", sep="")
        png(file.path(paste(getwd(),"//saida", sep=""),graphname))
               ans <- eval(parse(text=paste("plot(density(NNS.Delta.",i,"))",sep="")))
        dev.off()

        # Using boa package
        ans <- eval(parse(text=paste("boa.hpd(NNS.Delta.",i,", alpha = 0.05)",sep="")))
        write.csv2( ans , paste("HPD Diff ",i,".csv", sep=""))
        print( ans )

}

################################
# Sensitivity analysis - HAPO #
################################

# Screening strategies settings
LGA_Ptreatment <- rbeta(n, 40.5,  4.5 ) ; c <- 4.5; beta.parametros(9*c, 1*c, alfa) # melhor solução encontrada
LGA_logRRtreatment <- rnorm(n, -0.6095, 0.1245) ;   # A distribuição de log(RR)

PE_Ptreatment <- rbeta(n, 40.5,  4.5 ) ; c <- 4.5; beta.parametros(9*c, 1*c, alfa) # melhor solução encontrada
PE_logRRtreatment <- rnorm(n, -0.4903, 0.1413) ;    # A distribuição de log(RR)

CS_Ptreatment <- rbeta(n, 40.5,  4.5 ) ; c <- 4.5; beta.parametros(9*c, 1*c, alfa) # melhor solução encontrada
CS_logRRtreatment <- rnorm(n, -0.1100, 0.0797) ;           # A distribuição de log(RR)

# Common parameters settings
Pwho_HAPO <- 0.114
Piadpsg_HAPO <- 0.161
LGA_Iwhopos_HAPO <- 0.137
PE_Iwhopos_HAPO <- 0.076
CS_Iwhopos_HAPO <- 0.244
LGA_Iiadpsgpos_HAPO <- 0.162
PE_Iiadpsgpos_HAPO <- 0.091
CS_Iiadpsgpos_HAPO <- 0.244

# Compute incidence reduction - WHO
RI_LGA_WHO <- Pwho_HAPO * LGA_Iwhopos_HAPO * LGA_Ptreatment * (1-exp(LGA_logRRtreatment))
NNS_LGA_WHO <- 1 / RI_LGA_WHO

RI_PE_WHO  <- Pwho_HAPO * PE_Iwhopos_HAPO * PE_Ptreatment * (1-exp(PE_logRRtreatment))
NNS_PE_WHO <- 1 / RI_PE_WHO

RI_CS_WHO <- Pwho_HAPO * CS_Iwhopos_HAPO * CS_Ptreatment * (1-exp(CS_logRRtreatment))
NNS_CS_WHO <- 1 / RI_CS_WHO
```

```
# Compute incidence reduction - IADPSG
RI_LGA_IADPSG <- Piadpsg_HAPO * LGA_Iiadpsgpos_HAPO * LGA_Ptreatment * (1-exp(LGA_logRRtreatment))
NNS_LGA_IADPSG <- 1 / RI_LGA_IADPSG

RI_PE_IADPSG <- Piadpsg_HAPO * PE_Iiadpsgpos_HAPO * PE_Ptreatment * (1-exp(PE_logRRtreatment))
NNS_PE_IADPSG <- 1 / RI_PE_IADPSG

RI_CS_IADPSG <- Piadpsg_HAPO * CS_Iiadpsgpos_HAPO * CS_Ptreatment * (1-exp(CS_logRRtreatment))
NNS_CS_IADPSG <- 1 / RI_CS_IADPSG

# Save data
resultado.final.sa <- data.frame(
       "RI_LGA_WHO" = RI_LGA_WHO,
       "NNS_LGA_WHO" = NNS_LGA_WHO,
       "RI_PE_WHO" = RI_PE_WHO,
       "NNS_PE_WHO" = NNS_PE_WHO,
       "RI_CS_WHO" = RI_CS_WHO,
       "NNS_CS_WHO" = NNS_CS_WHO,

       "RI_LGA_IADPSG" = RI_LGA_IADPSG,
       "NNS_LGA_IADPSG" = NNS_LGA_IADPSG,
       "RI_PE_IADPSG" = RI_PE_IADPSG,
       "NNS_PE_IADPSG" = NNS_PE_IADPSG,
       "RI_CS_IADPSG" = RI_CS_IADPSG,
       "NNS_CS_IADPSG" = NNS_CS_IADPSG
       )

write.csv2( resultado.final.sa , "table_data_sensitivity analysis.csv" )

# Compute summary tables
tabela.resumo.sa <- array(,9)

vet.nomeselementos <- c("RI_LGA_WHO","NNS_LGA_WHO","RI_PE_WHO","NNS_PE_WHO","RI_CS_WHO","NNS_CS_WHO",
                        "RI_LGA_IADPSG", "NNS_LGA_IADPSG", "RI_PE_IADPSG", "NNS_PE_IADPSG", "RI_CS_IADPSG", "NNS_CS_IADPSG")

for (i in vet.nomeselementos) {
       ans <- eval(parse(text=i))
       tabela.resumo.sa <- rbind( tabela.resumo.sa, c( i, summary(ans), quantile(ans, probs = c(alfa/2, 1 - alfa/2), names = FALSE ) ) )
}

tabela.resumo.sa <- tabela.resumo.sa[ !is.na(tabela.resumo.sa[,1]) ,]

tabela.resumo.sa <- data.frame(tabela.resumo.sa)
names(tabela.resumo.sa) <- c("Estatística/Estratégia", names(tabela.resumo.sa)[2:(length(names(tabela.resumo.sa))-2)],
paste("Percentil ",round((alfa/2)*100, digits=1),sep=""), paste("Percentil ",round((1-alfa/2)*100, digits=1),sep=""))
```

```
write.csv2( tabela.resumo.sa , paste("Summary_AS_HAPO.csv", sep=""), row.names=FALSE )

# Summary - Highest Posterior Density Interval (HPD)
vet.nomeselementos1 <- c("RI_LGA_WHO","RI_PE_WHO","RI_CS_WHO","RI_LGA_IADPSG", "RI_PE_IADPSG", "RI_CS_IADPSG")
vet.nomeselementos2 <- c("NNS_LGA_WHO", "NNS_LGA_IADPSG","NNS_PE_WHO", "NNS_PE_IADPSG", "NNS_CS_WHO", "NNS_CS_IADPSG")
vet.nomeselementos <- c(vet.nomeselementos1, vet.nomeselementos2)

for (i in vet.nomeselementos) {
       print(paste("HPD Interval for ",i," | Sensitivity analysis HAPO",sep=""))

       graphname <- paste("grafico_AS_HAPO_",i,".png", sep="")
       png(file.path(paste(getwd(),"//saida", sep=""),graphname))
              ans <- eval(parse(text=paste("plot(density(",i,"))",sep="")))
       dev.off()

       ans <- eval(parse(text=paste("boa.hpd(",i,", alpha = 0.05)",sep="")))
       write.csv2( ans , paste("HPD Sensitivity analysis HAPO ",i,".csv", sep=""))
       print( ans )

}

dev.off()


# End of the syntax
####################
```

7. ARTIGO 3 – PREVALÊNCIA DO DIABETES MELLITUS GESTACIONAL DE ACORDO COM O CRITÉRIO DA IADPSG

Worldwide Prevalences of Gestational Diabetes Mellitus According to the IADPSG Criteria: a Systematic Review

[Revisão sistemática: Prevalência Global do Diabetes Mellitus Gestacional de Acordo com o Critério da IADPSG]

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A ser submetido ao periódico *Diabetologia*

SUMÁRIO - REVISÃO SISTEMÁTICA: PREVALÊNCIA GLOBAL DO DIABETES MELLITUS GESTACIONAL DE ACORDO COM O CRITÉRIO DA IADPSG

INTRODUÇÃO

Diabetes mellitus gestacional (DMG) é intolerância aos carboidratos, de intensidade variável, e com diagnóstico durante a gestação**.** Ao longo de cinco décadas, diferentes critérios foram propostos para o diagnóstico do DMG. Em 2010, a *International Association of Diabetes and Pregnancy Study Groups* (IADPSG) propôs um novo critério diagnóstico para o DMG, baseado nos resultados do estudo HAPO (*Hyperglycemia and Adverse Pregnancy Outcome).*

De acordo com a IADPSG, são classificadas como diabéticas as gestantes que apresentem alterados pelo menos um valor glicêmico no teste oral de tolerância a glicose (TOTG) com sobrecarga de 75g (jejum ≥92mg/dL; 1h ≥180mg/dL; 2hs ≥153mg/dL). Nos últimos três anos o critério da IADPSG vem ganhando importância, sendo adotado por diversas organizações, incluindo a *American Diabetes Association* (ADA**)**.

O objetivo desta revisão sistemática é estimar a prevalência do DMG de acordo com o critério da IADPSG e estimar o aumento relativo na sua prevalência quando comparado aos demais critérios diagnósticos atualmente em uso.

MÉTODOS

Delineamento: Revisão sistemática de estudos observacionais, com meta-análise

Busca: Doze diferentes bases eletrônicas (African index medicus; CENTRAL; EMBASE; IMEMR; IMSEAR; IndMED; ISI Web of Knowledge; KoreaMed; LILACS; Panteleimon; PubMed; and WPRIM **),** sendo realizada em dezembro de 2012;

adicionalmente foram avaliadas as listas de referências de artigos relevantes.

Seleção dos estudos: realizada independentemente por dois investigadores; incluídos estudos observacionais que avaliaram a prevalência do DMG de acordo com o IADPSG em população geral. Excluídos estudos de base hospitalar ou avaliando a prevalência em grupos de risco aumentado para o DMG.

Extração de dados: realizada independentemente por dois investigadores utilizando formulário padronizado para coleta de dados.

Análise de dados: dados agregados em meta-análise de efeitos aleatórios. Resultados apresentados em forma de proporção ou de razão de prevalência, com intervalos de confiança (IC) de 95%. Análises realizadas com o software *R* versão 2.1.11, pacote *Metafor 1.6-0.*

Avaliação da qualidade metodológica: Avaliação da qualidade da evidência (QdE) para o conjunto da evidência realizada de acordo com a abordagem do GRADE. Estudos individuais avaliados quanto ao risco de apresentarem viés de seleção e de aferição.

RESULTADOS

Inclusão dos estudos: Foram identificadas 171 referências, sendo selecionados 61 estudos para avaliar sua elegibilidade. Foram incluídos na revisão sistemática 20 publicações (referentes a 15 estudos), avaliando 71.730 gestações em 29 diferentes centros. Desses centros, nove encontravam-se no sul asiático/oriente médio, oito na Europa/região mediterrânea, seis na América do Norte, quatro na Austrália e dois na América Latina.

Prevalência do diabetes mellitus gestacional: a prevalência global estimada do DMG de acordo com o critério da IADPSG é de 18,7% (IC95% 15,8 – 21,7%; QdE baixa). A prevalência no sul asiático/oriente médio é de 19,3% (IC95% 12,2 – 27,6%; QdE muito

baixa); na Europa/região mediterrânea é de 19,7% (IC95% 15,4% - 24,3%; QdE baixa), na América do Norte é de 20,3% (IC95% 16,7 – 24,2%; QdE moderada); e na Austrália é de 14,8% (IC95% 11,4 a 18,5%; QdE moderada). Entre as mulheres com diagnóstico de DMG, a glicemia de jejum encontrava-se elevada em 60% dos casos (IC95% 53 – 68%), a glicemia 1h após o TOTG em 50% (IC95% 44 – 56%), e a glicemia 2hs após o TOTG em 38% (IC95% 33% - 44%).

Aumento relativo na prevalência do diabetes mellitus gestacional: a prevalência do DMG de acordo com o IADPSG é 53% (23 – 90%; QdE baixa) superior ao critério da Organização Mundial de Saúde (OMS) de 1999, 29% (4 – 61%; QdE baixa) superior ao critério da *Australian Diabetes in Pregnancy Society* (ADIPS) e 247% (167 - 351%; QdE baixa) superior ao critério da ADA vigente até 2010.

CONCLUSÕES

A prevalência do DMG de acordo com o critério da IADPSG é significativamente superior aos demais critérios diagnósticos. A adoção desse critério diagnóstico possui implicações econômica e na utilização de recursos, devendo isso ser considerado e avaliado a nível local para sua implementação.

Worldwide Prevalences of Gestational Diabetes Mellitus According to the IADPSG Criteria: a Systematic Review

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ABSTRACT

Aims: to estimate the prevalence of GDM according to the criteria proposed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and its increase when compared with frequently used criteria.

Methods: Twelve electronic databases and reference lists of relevant literature were searched for articles published from inception to December, 2012. Observational studies assessing the prevalence of GDM in general population were included. Independent extraction of articles was done by two authors using predefined data fields. Quality of evidence was assessed using GRADE.

Results: Data were obtained from 15 studies from 29 centers including 71,730 pregnant women. Using IADPSG criteria, estimated worldwide prevalence of GDM is 18.7% (95% CI 15.8 – 21.7%*) (low level of evidence*). Prevalence is 19.7% (15.4 – 24.3%) in Europe/Mediterranean region *(low level of evidence),* 19.3% (12.2 – 27. 6%) in South Asia/Middle East *(very low level of evidence),* 20.3% (16.7 – 24.2%) in North America *(moderate level of evidence)* and 14.8% (11.4 – 18.5%) in Australia *(moderate level of evidence)*. Among women classified as GDM, FPG was abnormal in 60.8% (53.1 – 68.3%), 1h-PG in 49.6% (43.6 – 55.7%) and 2h-PG in 37.6% (32.7 – 43.7%). Adopting the IADPSG criteria raises GDM prevalence by 53% (23 – 90%), 29% (4 – 61%) and 247% (167 – 351%) when compared to the 1999 WHO criteria, the ADIPS criteria and the former ADA criteria *(low level of evidence).*

Conclusion: The prevalence of GDM increases with the adoption of the IADPSG criteria for universal screening. Although based on variable (very low to moderate level) quality evidence, this increase in prevalence needs to be considered along with other public health implications for screening implementation.

Keywords

Diabetes, Gestational; IADPSG; Prevalence; Review, Systematic; Meta-Analysis.

Abbreviations

ADA	American Diabetes Association
ADIPS	Australian Diabetes in Pregnancy Society
BMI	Body mass index
CI	Confidence intervals
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
IADPSG	International Association of Diabetes in Pregnancy Study Groups
LGA	Large for gestational age
OGTT	Oral glucose tolerance test
PG	Plasma glucose
WHO	World Health Organization

BACKGROUND

Gestational diabetes mellitus (GDM) has been defined as glucose intolerance of variable severity with onset or first recognition during pregnancy. (1, 2) Although this definition has been largely accepted, the precise level of glucose intolerance characterizing GDM has been controversial for over three decades. Of note, the prevalence of GDM has increased markedly in recent years, in large part due to the obesity epidemic.(3)

The 1999 World Health Organization (WHO) diagnostic criteria for GDM were based on a fasting plasma glucose (FPG) ≥7.0 mmol/L (or 126 mg/dL) or a 2h plasma glucose (PG) ≥7.8 mmol/L (or 140 mg/dL) after a 75g glucose intake. (4, 5) The WHO did not revise GDM diagnostic criteria in 2006, but is currently specifically revising them. In 2010, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) proposed a new criteria, derived from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study,(6, 7) which has now been endorsed by the American Diabetes Association (ADA).(2) According to the IADPSG criteria, women with one or more of the following values are classified as having GDM: a fasting glucose ≥ 5.1 mmol/L (92 mg/dl) a one hour result of ≥ 10.0 mmol/L (180 mg/dl), or a two hour result of ≥ 8.5 mmol/L (153 mg/dl) after a 75g oral glucose tolerance test (OGTT). *(Table 1)*

Both criteria predict important adverse outcomes, such as large for gestational age (LGA) neonates and preeclampsia,(8) and screening approaches based on the new criteria seem to have a greater impact on the reduction of GDM associated outcomes.(9) This estimated benefit is mostly due to the expected major increase in the prevalence of GDM, leading screening and subsequent treatment to cost more, thus straining health system resources.

The aim of this study is to estimate the GDM prevalence according to the IADPSG criteria and to compare this prevalence with those of other criteria. We also assessed the quality of the evidence to support these prevalence estimates using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework adapted to prevalence studies within the screening context.

METHODS

Study selection

Type of studies

Cross-sectional studies and cohort studies were considered for inclusion if they provided sufficient information to estimate the prevalence of GDM with the IADPSG criteria in general populations. In order to avoid selection bias, we included only studies that applied the 75g OGTT to all participants. Studies applying the OGTT only in women with certain clinical risk factors (such as family history, obesity, previous GDM) or in those positive in pre-OGTT glucose screening (e.g. 50g-glucose challenge test) were excluded.

Types of diagnostic tests

Only studies based on a 2 hour 75 g OGTT, with values of plasma glucose at fasting, 1h and 2h after glucose load, performed during the 2nd or the 3rd trimesters were included. Studies extrapolating results from 100g OGTT or using 75g OGTT without all three glucose measures were considered only for a pre-specified sensitivity analysis.

Outcomes measures

Main outcome was the prevalence of GDM according to the IADPSG criteria. We also evaluated the proportion of participants with abnormal fasting, 1h and 2h PG during an OGTT. In addition, we evaluated the increase in the prevalence of GDM when compared with other criteria based on a 75g-OGTT.

Search strategy

We searched 12 electronic databases (African index medicus; CENTRAL;; EMBASE; IMEMR; IMSEAR; IndMED; ISI Web of Knowledge; KoreaMed; LILACS; Panteleimon; PubMed; and WPRIM) for articles published from inception up to December 6th, 2012. In our search, we used the following terms: IADPSG and "International Association of Diabetes in Pregnancy Study Groups" *(appendix 1)*

Data collection and analysis

Selection of studies

All citations identified were entered into an electronic database and duplicates were deleted. Initially, two investigators independently screened titles and abstracts of potentially relevant studies to assess eligibility. When the information was not sufficient to determine if the article was eligible for inclusion, the article's full text was obtained for evaluation. Discrepancies were solved through discussion.

Data extraction and management

Two independent investigators reviewed the eligible studies and abstracted data using a standardized form prepared for this review. Information extracted from each individual trial consisted of:

(1) study characteristics: authors, year, number of centers, location, design, data collection, data source, patients screened, patients included, reasons for not participating;

(2) population characteristics: ethnicity, mean age, mean body mass index (BMI) and mean gestational age at OGTT;

(3) test: glucose sample (plasma or capillary), method of analysis and laboratory quality control;

(4) outcomes: proportion of women with GDM according to the IADPSG criteria, to the 1999 WHO criteria, the Australian Diabetes in Pregnancy Society (ADIPS) criteria and the former ADA criteria; proportion of women with abnormal fasting, 1h and 2h glucose during an OGTT (according to the IADPSG cut-offs). For studies not presenting FPG cut-offs for the 1999 WHO criteria, we considered positive women reaching the 2h-PG≥140 mg/dL, since few cases meet the 1999 WHO criteria based solely on the fasting value..

When a study was performed in different regions, whenever possible, data were abstracted separately and each center was considered a different study. Disagreements were solved through discussion until consensus was reached. When raw quantitative data were not reported, approximate values were obtained from figures or calculated from percentages.

Assessment of risk of bias and overall quality of a body of evidence

The risk of bias of the included studies was assessed by examining the following factors in each study:

(1) Data source (e.g. primary data, laboratory records, medical records, national databases), adequate description of excluded screened participants and exclusion of prior diagnosis of diabetes

(2) Standardization of the glucose tolerance test (sample type and description of laboratory quality control)

Studies describing well the population source (representing an unselected population) were considered as low risk of selection bias. Examples include specification of consecutive sampling, indications of a general antenatal care or a population based care. Studies performed in a high risk setting, such as tertiary care obstetric clinics, were considered as high risk of bias.

To assess the quality of the body of evidence, we used the GRADE framework, adapted to evaluate data from prevalence studies. The following domains were considered: study limitations, inconsistency, indirectness, imprecision and publication bias, using a similar approach developed for baseline risk assessment.(10) A methodological article applying GRADE for prevalence questions is under development.

Data synthesis and statistical analysis

Data for prevalence of GDM with IADPSG criteria and the proportion of impaired values for each cut-off were pooled and presented as proportions with 95% confidence intervals (CI). Prevalence increase with the IADPSG criteria, compared with other criteria, was presented as prevalence ratio with 95% CI. Proportions were transformed using Freeman-Tukey double arcsine procedure and meta-analysis was performed employing the

random-effects model (*DerSimonian and Laird*). Subgroup analysis was performed based on the geographic region.

For sensitivity analysis, data were combined employing both fixed and random effects model to check for consistency of data. Additional analyses were performed including studies applying modified-IADPSG criteria (without 1h-PG values). For GDM prevalence, we performed a subgroup analysis according to the risk of selection bias and meta-regression mean according to maternal age, mean BMI at OGTT , mean gestational age at OGTT and proportion of individual with impaired fasting glucose (in order to explore the possibility of incomplete fasting). Statistical analyses were performed using the R version 2.11.1 software, package *Metafor* version 1.6-0.(11)

RESULTS

After excluding duplicates, our search identified 171 references. We reviewed all titles and abstracts, identifying 61 potentially relevant studies to be assessed by full text. A total of 20 publications pertaining to 15 studies met the selection criteria and were included in the main analysis of this systematic review which included 71,730 pregnant women. The degree of concordance among reviewers for selection of potential studies and inclusion of the studies was high (*kappa*=0.88, 95%CI 0.81 to 0.95, and *kappa*=0.85, 95%CI 0.71 to 0.99 respectively).

Prevalence data were available for each center of the HAPO study (n=15) (6, 12) and evaluated separately as a single study. In total we had data from 29 different centers *(Supplementary Figure 1).* The main characteristics of included studies are presented in Table 2. Nine studies were conducted in the south Asia and Middle East region, eight in

Europe and in the Mediterranean region, six in North America, four in Australia, and two in Latin America. *(Figure 1, Table 2)*

Four studies were identified which applied modified IADPSG criteria (without results for 1h-PG after OGTT) and were included in a pre-specified sensitivity analysis.(13-16) *(Appendix 2, supplementary Table 1)* List of excluded studies and reasons for exclusion are available in the *Appendix 3.*

Methodological quality

Of the 15 studies, ten presented low risk of selection bias. (6, 12, 17-25) Risk of selection bias was considered unclear in four studies (26-30) and high in only one study.(31) Adequate description of exclusions was reported in 7 studies (6, 19, 20, 22, 26, 28, 32) and description of laboratory control process in 7 studies. (6, 18-20, 22, 26, 27) Plasma glucose was probably used in all studies. Assessment of the methodological quality of studies included is summarized in the *supplementary Table 2*. Evidence profiles for the quality assessment according to GRADE are presented in T*ables 3 and 4*.

Prevalence of GDM

The estimated worldwide prevalence of GDM according to the IADPSG criteria is 18.7% (95% CI 15.8 – 21.7%*) (low level of evidence*). The prevalence is 19.7% (15.4 – 24.3%) in Europe/Mediterranean region *(low level of evidence)* 19.3% (12.2 – 27.6%) in South Asia/Middle East *(very low level of evidence)*, 20.3% (16.7 – 24.2%) in North America *(moderate level of evidence)* and 14.8% (11.4 – 18.5%) in Australia *(moderate level of evidence)* (Figure 2). Among women with GDM, FPG was abnormal in 60.8% (53.1 – 68.3%), 1h-PG in 49.6% (43.6 – 55.7%) and 2h-PG in 37.6% (32.7 – 43.7%). *(supplementary Figures 5, 6 and 7; supplementary Table 5)*

Prevalence increase of GDM

Higher prevalence of GDM was observed with the IADPSG criteria. The relative increase in GDM prevalence according to the IADPSG criteria was 53% (95% CI 23 – 90%) higher than with the 1999 WHO criteria, 29% (4 – 61%) higher than with the ADIPS criteria and 247% higher than with the former ADA criteria (167 – 351%) *(moderate level of evidence) (Figure 3).* The absolute increase worldwide would be 6.5% (3.5- 8.9%), 4.2% (0.7 – 7.1%) and 13.3% (11.7 – 14.6%) when compared with the 1999 WHO criteria, the ADIPS criteria and the former ADA criteria, respectively.

Sensitivity analysis.

The inclusion of studies applying modified-IADPSG criteria did not significantly change the overall GDM prevalence (18.9% vs. 18.7%) (*supplementary Figure 2*). A higher prevalence of GDM was observed in studies with high or unclear risk of selection bias compared with those at low risk of bias (26.9% vs. 17.4%) *(supplementary Figure 3).* In general, results were consistent among fixed and random effects models, except for the prevalence in South Asia / Middle East (19.3% and 25.9% with random and fixed effects models, respectively). (*Data available upon request*)

Four studies compared a modified-IADPSG criteria with the 1999 WHO criteria, including only fasting and 2h values. Although a decrease in the prevalence would be expected given that these studies had only two measurement points, their prevalences were in fact higher. Thus, their exclusion in the analysis decreased slightly the relative increase in GDM prevalence with the IADPSG criteria (65% vs. 53%) *(supplementary Figure 4; supplementary Table 4)*

Meta-regression did not show a statistically significant influence of mean maternal age (p=0.87), mean gestational age at OGTT (p=0.89), mean BMI at OGTT (p=0.34) and proportion of GDM women with impaired FPG (p=0.27). (s*upplementary Figure 8*). Funnel plot showed no clear evidence of publication bias, although a small asymmetry was observed in the plot for the increase in prevalence with the IADPSG criteria compared to the 1999 WHO. *(supplementary Figures 9 and 10)*

DISCUSSION

The prevalence of GDM is expected to be high – 18.6%, almost one out of five pregnant women – with the adoption of the IADPSG criteria. This estimate was generated from a large worldwide sample of pregnant women. For some areas, the prevalence will be higher than 30%. Of note, for only 2 of the 29 sites evaluated prevalence lower than 10%. The estimated increase in prevalence is estimated in 53%, 29% and 247% when compared to the 1999 WHO, the former ADA and the ADIPS criteria, respectively.

Interestingly, more than 60% of GDM pregnancies were diagnosed with the FPG. A two-steps screening starting with FPG, as proposed by Agarwal,(33) may be useful in such settings . However, it is important to keep in mind that the evidence to support the effectiveness of gestational diabetes screening is based on diagnostic criteria involving at least one post glucose load value. Additionally, in settings with a lower proportion of GDM diagnosed by FPG (e.g. Indian subcontinent), this strategy will not be useful.(34)

This is, to our knowledge, the first systematic review evaluating the prevalence of GDM according to the IADPSG criteria, adopted by important organizations such as the ADA and, more recently, the WHO. We combined data from 15 studies, including data from 29 centers, with more than 70,000 women. We provided estimates for different

regions and the expected increase when compared with previous GDM criteria based on the 75g test, assessing the quality of evidence using an adaptation of the GRADE approach. We expect that our contribution may help policy makers when planning and implementing public health strategies since it provides relevant data for estimating the burden of disease and, consequently, the use of resources.

Our study has some limitations; important heterogeneity was observed across studies, which may impact on the confidence of our estimates. Also, most studies were conducted in developed countries; regions like Asia, Africa and Latin America were under-represented. Prevalence based on the 1999 WHO criteria was not uniform across studies; differences in the fasting plasma glucose thresholds may impact in the estimated prevalence increase when comparing to the IADPSG criteria, however, as the diagnosis of GDM in most of cases is likely to be due to the 2h-plasma value, we expect that the overall influence of the specific cut off for the fasting value should be low. Since our meta-analysis was based on aggregated data, we were unable to identify factors that may explain differences in the prevalence across regions, such as ethnicity, mean maternal age and BMI. Nevertheless, based on data from individual studies, these factors appear to have an important role in the overall prevalence.(20, 35)

Important criticisms about previous GDM diagnostic criteria are that they were not derived from relevant pregnancy outcomes,(36) or were adapted from criteria for diabetes in non-pregnant population.(5) The IADPSG criteria were based on the prediction of pregnancy related outcomes, using the HAPO study population, a large multicenter, multiethnic, well designed cohort study.(6) Although the IADPSG criteria were based on surrogate outcomes (large for gestational age births, cord C-peptide and body fat), a similar increase in risk was seen when applying these criteria for clinically

important pregnancy-related outcomes, such as macrosomia, preeclampsia and caesarean section. (8, 32, 35)

Based on these recent studies, currently several societies and organizations are reviewing their criteria for GDM. ADA in 2011 endorsed the IADPSG criteria; other important organizations, including WHO and the International Federation of Gynecology and Obstetrics (FIGO), are expected to update their recommendations in the upcoming months. However there is no consensus about decisions and by now it seems that we are far from having an unified criteria. In March 2013, the NIH decided to not endorse the IADPSG criteria; panel members considered that sufficiently clear evidence of substantial benefits from the IADPSG approach is lacking to justify a change in the diagnostic technique. Furthermore, they expressed their concern that this strategy would increase the number of women labeled as GDM two- to threefold, which could increase substantially personal and societal costs.

Even though treatment of GDM is effective in the prevention of pregnancy-related outcomes,(37, 38) the overall population benefit is only modest. Universal screening based on IADPSG criteria has been estimated to reduce the overall incidence of LGA births by 0.85% (NNS = 117) and of preeclampsia by 0.39% (NNS = 257).(9) The increase in costs and resources needed with the adoption of the IADPSG criteria is of important concern.(39-41) A cost-utility analysis found that screening based on the IADPSG criteria was not cost-effective unless long term maternal benefits were also considered.(42) Another recent cost-utility analysis compared this new screening strategy with universal screening according to current American Congress of Obstetricians and Gynecologist guideline (1-h glucose challenge test followed by a 3-h OGTT) finding that the screening strategy based on the IADPSG criteria may be cost-effective for high resources settings ($61,503/QALY), but probably is too costly for most countries.(43)

Another analysis, which also considered post-partum interventions for diabetes prevention, concluded that GDM screening based on the IADPSG criteria is highly cost-effective in Israel and India. (44)

The high prevalence of GDM is an important barrier for the implementation of public health programs based on the IADPSG criteria. Of note, studies estimating its prevalence in low-income countries are lacking. Alternative strategies, such as selective screening and two-steps diagnostic approach should be developed, taking in consideration population and economic characteristics; is important to state that any local adaptation will need to rely on accurate local data of the population under consideration.(45)

In sum, the adoption of the IADPSG criteria will substantially increase the prevalence of GDM. While adopting these criteria, economic implications are likely to be important. Thus, costs and resources should be considered and evaluated in such settings.

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MF wrote the protocol, researched and analyzed data and wrote the manuscript. MS researched data and reviewed the protocol and the manuscript. BBD, GR, HJS and SC contributed to discussion and reviewed the protocol and the manuscript. MIS participated in all the aspects of the project and was the overall supervisor.

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Table 1 - Most used diagnostic criteria of GDM based on 75g OGGT

Criteria	Diagnosis
IADPSG / ADA	GDM defined as at least one value meeting the thresholds: - Fasting plasma glucose ≥92mg/dL (≥5.1 mmol/L) - 1-h plasma glucose ≥180mg/dL (≥10.0 mmol/L) - 2-h plasma glucose ≥153mg/dL (≥8.5 mmol/L)
Former ADA criteria (up to 2010)	GDM defined as at least two values meeting the thresholds: - Fasting plasma glucose ≥95mg/dL (≥5.3 mmol/L) - 1-h plasma glucose ≥180mg/dL (≥10.0 mmol/L) - 2-h plasma glucose ≥155mg/dL (≥8.6 mmol/L)
1999 WHO[1]	GDM defined as diabetes or impaired glucose tolerance • Diabetes defined as at least one value meeting the threshold: - Fasting plasma glucose ≥ 126 mg/ dL (≥ 7.0 mmol/L)[1] - 2-hour plasma glucose ≥200 mg/dL (≥ 11.1 mmol/L) • Impaired glucose tolerance defined as: - Fasting plasma glucose < 126 mg/ dL (≥ 7.0 mmol/L) - 2-hour plasma glucose ≥140 mg/dL (≥ 7.8 mmol/L)
ADIPS	Diabetes defined as at least one value meeting the threshold: - Fasting plasma glucose ≥ 100 mg/ dL (≥ 5.5 mmol/L) - 2-hour plasma glucose ≥145 mg/dL (≥ 8.0 mmol/L)

Adapted from *Tran et al 2013* (21)

GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; IADPSG: International Association of Diabetes in Pregnancy; ADA: American Diabetes Association; WHO: World Health Association; ADIPS: Australian Diabetes in Pregnancy Society

[1] Some authors consider fasting plasma glucose of 110mg/dL (6.1 mmol/L) or ≥ 100 mg/ dL (≥ 5.5 mmol/L) as a threshold for diabetes.

Table 2.Prevalence of gestational diabetes mellitus (GDM) and characteristics of included studies

Study / Country	Year of recruitment	Risk of selection bias [1]	n	Ethnicity %	Maternal age (years) mean (SD)	Gestational week at OGTT: mean (SD)	BMI at OGTT [2] mean (SD)	GDM (IADPSG) %
Agarwal 2010(27) UAE	2003-2008	Unclear	10,283	Arabs 80.1; Indian subcontinent[3] 15.5	28.3 (6.1)	25.3 (6.3)	NR	37.7
Agarwal 2012(26) UAE	2008-2009	Unclear	849	Arabs 76.7; Indian subcontinent[3] 16.5	29.4 (6.0)	27.0 (6.4)	NR	32.9
Black, 2013(35) USA, Florida	2005-2010	Low	10,459	NR	NR	NR	NR	24.1
Corrado 2012(28) Italy	2010-2011	Unclear	738	Caucasian 100	30.8 (5.2)	25.9 (2.7)	24.1 (7.3) [4]	11.9
Dahanayaka 2012(18) Sri Lanka	NR	Low	405	NR	27.3 (5.4)	24-28: 81.5% 29-32: 17.8% >32: 0.7%	>25: 19.3%[4]	8.9
EBDG 2001(19, 46) Brazil	1991-1995	Low	4,998	White: 44.9 Mixed: 44.1 Black: 13.6	27.8 (5.5)	24 – 28 [5]	23.4 (4.0)[1]	18.3
HAPO 2008(6, 12, 47) Multicountry	2000-2006	Low	23,957	White: 48.3 Black: 11.6 Hispanic: 29 Asian: 2.6	29.3 (5.8)	24 – 32 [5]	27.8 (5.2)	17.8
- Bellflower, USA	NR	Low	1,981	NR	29 (5.5)	24 – 32 [5]	30.1 (5.6)	25.5
- Singapore	NR	Low	1,787	NR	31.3 (5.9)	24 – 32 [5]	27.2 (4.7)	25.1
- Cleveland, USA	NR	Low	797	NR	27.8 (5.9)	24 – 32 [5]	29.5 (6.2)	25
- Manchester UK	NR	Low	2,376	NR	30.0 (5.6)	24 – 32 [5]	29.1 (5.5)	24.3
- Thailand	NR	Low	2,499	NR	28.0 (5.6)	24 – 32 [5]	25.7 (3.6)	23
- Chicago, USA	NR	Low	753	NR	32.8 (3.9)	24 – 32 [5]	27.4 (4.4)	17.3
- Belfast, UK	NR	Low	1,671	NR	29.7 (5.5)	24 – 32 [5]	28.4 (4.8)	17.1
- Canada	NR	Low	2,028	NR	33.6 (4)	24 – 32 [5]	27.8 (4.9)	15.5
- Providence, USA	NR	Low	757	NR	25.4 (5.5)	24 – 32 [5]	29.5 (6.4)	15.5
- Newcastle, AU	NR	Low	668	NR	29.5 (5.5)	24 – 32 [5]	29.6 (6.0)	15.3
- Hong Kong, China	NR	Low	1,654	NR	30.7 (4.9)	24 – 32 [5]	24.5 (3.0)	14.4
- Brisbane, AU	NR	Low	1,444	NR	29.4 (5.3)	24 – 32 [5]	28.9 (5.6)	12.4
- Barbados	NR	Low	2,093	NR	25.8 (5.9)	24 – 32 [5]	27.9 (5.9)	11.9
- Petah-Tiqva, Israel	NR	Low	1,818	NR	28.0 (5.5)	24 – 32 [5]	26.7 (4.5)	10.1
- Beersheba, Israel	NR	Low	1,631	NR	27.7 (5.4)	24 – 32 [5]	27.3 (4.5)	9.3
Hirst 2012(20, 21) Vietnam	2010-2011	Low	2,772	Vietnamese 95	28.3 (4.8)	28.7 (1.8)	20.6 (2.7)[4]	20.4
Huynh 2011(31) Melbourne, AU	2005-2007	High	5,473	NR	NR	NR	NR	18.7
Karatodorova 2011(29) Bulgaria	2007-2010	Low	299	NR	28.9 (4.4)	27.4 (3.5)	>26 (18%)[4]	34.5
Kun 2013(30) Hungary	2010-2011	Low	1,080	NR	29.6 (5.4)	NR	25.6 (6.0) [4]	16.4
Lacaria 2013(25) Italy	2010-2011	Low	2,274	Caucasian	NR	NR	NR	18.9
Moses 2011(22) Wollongong, AU	2010	Low	1,275	NR	30.0	NR	NR	13
O'Sullivan 2011(32) Ireland	2006-2009	Low	5,500	European 92.9	31.5 (5.5)	24 – 28 [5]	26.9 (5.1) [4]	12.4
Savona-Ventura 2012(23, 24) Mediterranean region	NR	Unclear	1,368	NR	30.1 (5.6)	24 – 32 [5]	28.2 (5.1)	26.6

N: number of participants; SD: standard deviation; BMI: body mass index. OGTT: oral glucose tolerance test, GDM: gestational diabetes mellitus, IADPSG: International Association of Diabetes and Pregnancy Study Groups , UAE: United Arab Emirates; NR: not reported; AU: Australia; USA: United States of America; UK: United Kingdom.

[1] Risk of selection bias is defined as low, unclear or high. Studies describing well the population source (representing an unselected population) were considered as with low risk of bias); high risk of bias represents studies with higher risk of selecting participants with higher probability of having GDM (e.g. laboratory databases, hospital-based studies)

[2] kg/m^2

[3] Indian subcontinent: India, Pakistan, Bangladesh and Sri Lanka

[4] BMI: pre-pregnancy or at first antenatal visit

[5] Range

[6] 11 countries: Mediterranean region (France, Greece, Italy, Malta, Portugal, Serbia: n=827); Maghreb region (Algeria, Morocco, Tunisia; n=361); Middle Eastern shore (Lebanon, Syria n=180)

Table 3 – Evidence profile: prevalence of GDM according to the IADPSG criteria

Population: general population (uncomplicated pregnancies)
Outcome (condition): GDM according to the IADPSG criteria

Outcome	Studies[1]; sample	Risk of bias	Inconsistency	Indirectness	Imprecision	Other factors	Summary prevalence (95%CI)	Quality of evidence
GDM (overall)	29 studies; n=71,730	None	Serious inconsistency[2]	Serious indirectness[3]	Not serious	None	18.7% (15.8 – 21.7%)	⊕⊕◯◯ Low
GDM in South Asia/Middle East	9 studies; n=23,398	None	Very serious inconsistency[2]	Serious indirectness[4]	Not serious	None	19.3% (12.2 – 27.6%)	⊕◯◯◯ Very Low
GDM in North-America	6 studies; n=17,775	None	Not serious	Serious inconsistency[4]	Not serious	None	20.3% (16.7 – 24.2%)	⊕⊕⊕◯ Moderate
GDM in Europe/ Mediterranean region	9 studies; n=15,306	None	Serious inconsistency[2]	Serious indirectness[4]	Not serious	None	19.7% (15.4 – 24.3%)	⊕⊕◯◯ Low
GDM in Australia	4 studies; n=8,860	Serious[5]	Not serious	Not serious	Not serious	None	14.8% (11.5 – 18.5%)	⊕⊕⊕◯ Moderate

GDM: gestational diabetes mellitus; IADPSG: International Association of Diabetes in Pregnancy Study Groups; CI: confidence interval; n: number of participants
[1] Each HAPO study center was considered as an individual study.
[2] Wide range of prevalence among studies, especially in South Asia centers, showing important differences among fixed and random effects models
[3] Important areas under-represented, such as Latin America, Africa and Asia.
[4] Important areas under-represented.
[5] Study at high risk of selection bias presented a larger sample size and a high prevalence (18.7%)

Table 4 – Evidence profile: increase in GDM prevalence with the IADPSG criteria when compared to other criteria.

Population: general population (uncomplicated pregnancies)
Outcome (condition): GDM according to the IADPSG criteria
Comparison (condition): GDM according to the different diagnostic criteria

Outcome	Reference for comparison	Studies; sample	Risk of bias	Inconsistency	Indirectness	Imprecision	Other factors	Relative increase (95% CI)	Absolute increase (95%CI)[1]	Quality of evidence
Increase in GDM prevalence	1999 WHO criteria	9 studies; n=41,070	None	Serious inconsistency[2]	Not serious	Not serious	Publication bias[3]	53% (23 - 90%)	6.5% (3.5% - 8.9%)	⊕⊕⊕○ Low
	ADIPS criteria	4 studies; n=10,369	None	Serious inconsistency[2]	Not serious	Serious[4]	None	29% (4 – 61%)	4.2% (0.7 – 7.1%)	⊕⊕⊕○ Low
	Former ADA criteria	6 studies; n=20,569	None	Serious inconsistency[2]	Not serious	Serious[4]	None	247% (167 – 351%)	13.3% (11.7 – 14.6%)	⊕⊕⊕○ Low

GDM: gestational diabetes mellitus; IADPSG: International Association of Diabetes in Pregnancy Study Groups; WHO: World Health Organization; ADIPS: Australian Diabetes in Pregnancy Society; ADA: American Diabetes Association; CI: confidence interval; n: number of participants
[1] For a estimate worldwide prevalence of 18.7% according to the IADPSG criteria
[2] Wide range of prevalence ratio among studies
[3] Possible publication bias as some studies with higher increase in prevalence of GDM were not included in the analysis because they lacked the 1h-plasma glucose.
[4] Wide confidence intervals

Figure legends

Figure 1: Prevalence (%) of gestational diabetes mellitus according to the individual studies

Figure 2: Worldwide prevalences of gestational diabetes mellitus according to the IADPSG criteria

Footnotes:
GDM: gestational diabetes mellitus; CI: confidence interval; IADPSG: International Association of Diabetes in Pregnancy; UAE: United Arab Emirates; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois

Figure 3: Increase in the prevalence of gestational diabetes mellitus with the IADPSG criteria compared to other criteria

Footnotes:
IADPSG: International Association of Diabetes in Pregnancy; PR: prevalence rate; ADA: American Diabetes Association; WHO: World Health Association; ADIPS: Australian Diabetes in Pregnancy Society
Fasting plasma glucose(FPG) criterion varies for 1999 WHO criteria. Hirst 2012, EBDG 2001, Karatadova 2010, Agarwall 2012 and Dahanayaka 2012 considered FPG≥126mg/dL (≥7.0mmol/dL) as threshold; O'Sullivan 2011 considered FPG≥110mg/dL (≥6.1mmol/dL) as threshold. FPG was not considered in the HAPO study for estimate the prevalence according to the 1999 WHO criteria; Kun 2013 and Savona-Ventura 2012 does not describe the threshold considered. "

Supplementary figures

Supplementary figure 1. Flow diagram of literature search and study selection

Supplementary figure 2: Sensitivity analysis – prevalence of gestational diabetes mellitus including studies with modified IAPDSG criteria

Supplementary figure 3: Sensitivity analysis – prevalence of gestational diabetes mellitus according to the risk of selection bias

Supplementary figure 4: Sensitivity analysis – prevalence increase of gestational diabetes mellitus with the IADPSG criteria compared to the 1999 WHO, including studies with modified IADPSG criteria

Supplementary figure 5: Proportion of pregnancies with gestational diabetes mellitus according to the IADPSG criteria presenting impaired fasting plasma glucose (>=92mg/dL)

Supplementary figure 6: Proportion of pregnancies with gestational diabetes mellitus according to the IADPSG criteria presenting impaired 1h-plasma glucose (>=180mg/dL)

Supplementary figure 7: Proportion of pregnancies with gestational diabetes mellitus according to the IADPSG criteria presenting impaired 1h-plasma glucose (>=153mg/dL)

Supplementary figure 8: Sensitivity analysis - meta-regression of the association of GDM prevalence and study's factors (proportion of women with impaired fasting plasma glucose, mean maternal age, mean BMI at OGTT and mean gestational age at OGTT)

Supplementary figure 9: Assessment of publication bias – funnel plot for the prevalence of gestational diabetes mellitus

Supplementary figure 10: Assessment of publication bias – funnel plot for the Prevalence increase of Gestational Diabetes Mellitus with the IADPSG criteria compared to the 1999 WHO

Figure 1: Prevalence (%) of gestational diabetes mellitus according to the individual studies

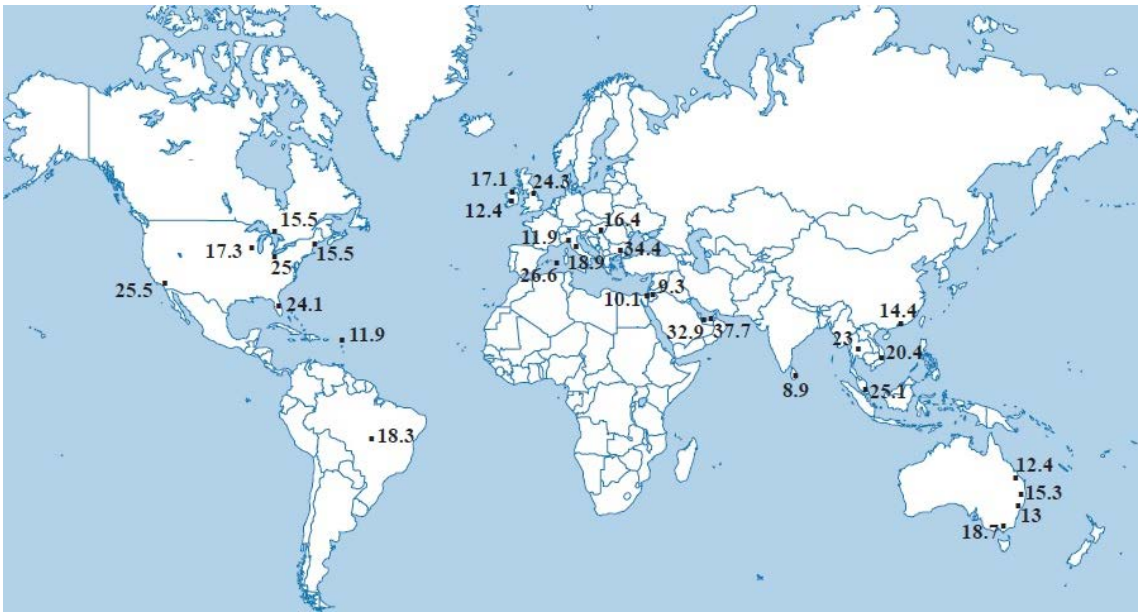
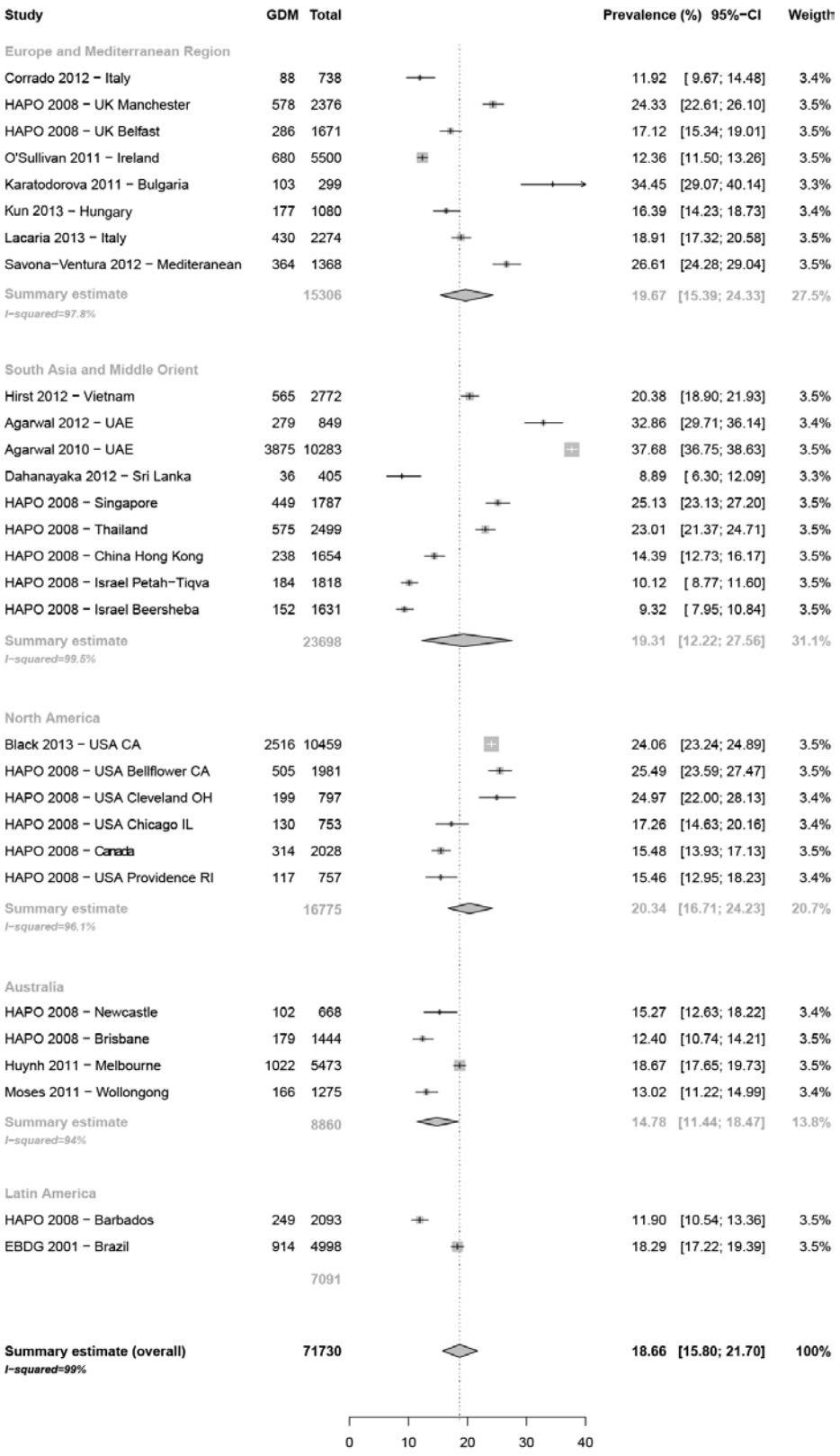
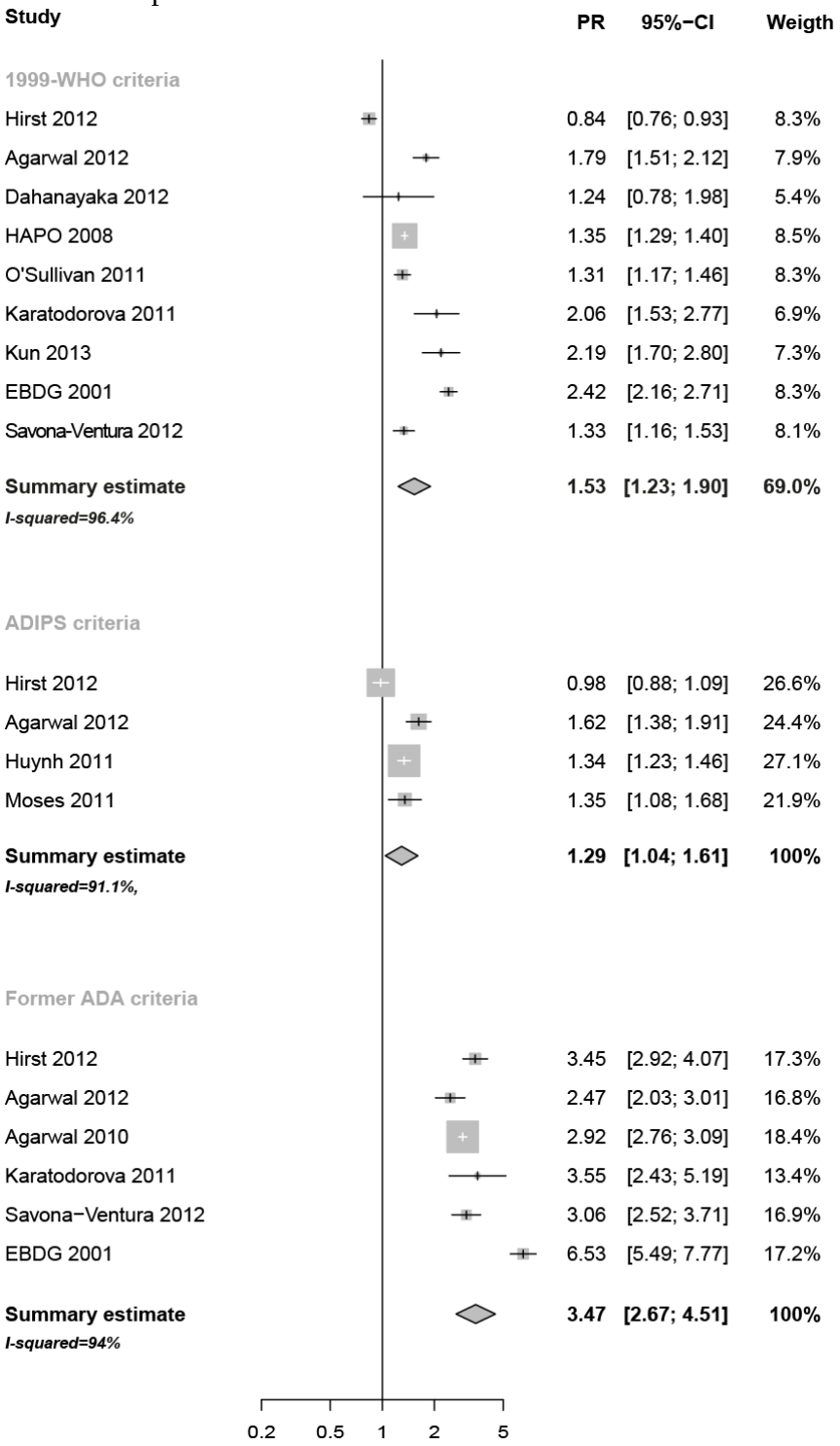


Figure 2: Worldwide prevalences of gestational diabetes mellitus according to the IADPSG criteria



GDM: gestational diabetes mellitus; CI: confidence interval; IADPSG: International Association of Diabetes in Pregnancy; UAE: United Arab Emirates; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois

Figure 3: Increase in the prevalence of gestational diabetes mellitus with the IADPSG criteria compared to other criteria



IADPSG: International Association of Diabetes in Pregnancy; PR: prevalence rate; ADA: American Diabetes Association; WHO: World Health Association; ADIPS: Australian Diabetes in Pregnancy Society Fasting plasma glucose(FPG) criterion varies for 1999 WHO criteria. Hirst 2012, EBDG 2001, Karatadova 2010, Agarwall 2012 and Dahanayaka 2012 considered FPG≥126mg/dL (≥7.0mmol/dL) as threshold; O'Sullivan 2011 considered FPG≥110mg/dL (≥6.1mmol/dL) as threshold. FPG was not considered in the HAPO study for estimate the prevalence according to the 1999 WHO criteria; Kun 2013 and Savona-Ventura 2012 does not describe the threshold considered.

Supplementary materials (online only)

Supplementary table 1.Prevalence of gestational diabetes mellitus (GDM) and characteristics of studies applying modified-IADPSG criteria (1h-OGTT plasma glucose values missing)

Study / Country	Year of recruitment	Risk of selection bias [1]	N	Ethnicity	Maternal age (years) mean (SD)	Gestational week at OGTT: mean (SD)	BMI[2] mean (SD)	GDM (IADPSG)
Bachaoui 2011 Algeria	NR	Unclear	1,680	NR	29.2 (4.7)	NR	25.48 (5.3)[3]	19.6%
Jenum 2012 Norway	2008-2010	Low	759	Western Europe 41.2% Eastern Europe 5.5% South Asia 24.8% East Asia 5.1% Middle East 14.8% Somalia 4.6% Sub-Saharan Africa/ South America: 4%	29.9 (4.8)	28 (1.3)	24.6 (4.8)[4]	31.5%
Kun 2011 Hungary	2000	Low	1,835	NR	26.5 (4.9)	24 – 28[4]	23.4 (4.5)[4]	16.6%
Richardson 2011 UK	2010-2011	High	1,070	NR	NR	NR	NR	17.5%

N: number of participants; SD: standard deviation; BMI: body mass index. OGTT: oral glucose tolerance test, GDM: gestational diabetes mellitus; NR: not reported IADPSG: International Association of Diabetes and Pregnancy Study Groups; UK: United Kingdom.

[1] selection bias is defined as low, unclear or high. Studies describing well the population source (representing an unselected population) were considered as with low risk of bias); high risk of bias represents studies with higher risk of selecting participants with higher probability of having GDM (e.g. laboratory databases, hospital-based studies)
[2] kg/m2
[3] Unknown moment of BMI measurement
[4] BMI: pre-pregnancy or at first antenatal visit
[5] Range

Supplementary table 2: Quality assessment of included studies

Study	Data source	Excluded previous DM	Adequate description of exclusions[1]	Glucose[2] / method	Description of laboratory control process	Risk of selection bias [3]
Agarwal 2010	Routine antenatal clinics of two tertiary care hospitals.	NR	No	Plasma, oxidase	Yes	Unclear
Agarwal 2012	Routine antenatal clinics of a tertiary care hospital	Yes	Yes	Plasma, oxidase	Yes	Unclear
Black, 2013	Population-based: Kaiser Permanente Southern California Medical Care Program	NR	No	Plasma	No	Low
Corrado 2012	All consecutive Caucasian women scheduled for an OGTT in the Department of Obstetrics and Gynecology of a University Hospital	Yes	Yes	Plasma	No	Unclear
Dahanayaka 2012	3 Medical Office Areas (centers)	NR	No	Plasma, oxidase	Yes	Low
EBDG 2001	Prenatal care clinics in 6 cities	Yes	Yes	Plasma, oxidase	Yes	Low
HAPO 2008	Population based – 15 centers in 9 countries	Yes	Yes	Plasma, oxidase	Yes	Low[4]
Hirst 2012	Local and referral women hospital	Yes	Yes	Plasma, hexokinase	Yes	Low
Huynh 2011	Laboratory records: Austin Pathology Database	NR	No	Plasma	No	High
Karatodorova 2011	Population-based, one university hospital	Yes	No	Plasma	No	Low
Kun 2013	Primary, all pregnant women in the Szekszárd region of Hungary	NR	No	NR[5]	No	Low
Lacaria 2013	Women undergoing universal screening in Tuscany region	NR	No	Plasma	No	Low
Moses 2011	Public hospital and private clinics in Wollongong	NR	Yes	Plasma, hexokinase	Yes	Low
O'Sullivan 2011	Women from 5 obstetric centers submitted to universal screening	NR	Yes	NR[5]	No	Low
Savona-Ventura 2012	Convenient sample of 75-200 pregnant women per participating center	Yes	No	NR[5]	No	Unclear

DM: diabetes mellitus; NR: not reported; OGTT: oral glucose tolerance test

[1] Study reports number of participants and reasons for nonparticipation of eligible women
[2] Plasma or capillary
[3] Selection bias is defined as low, unclear or high. Studies describing well the population source (representing an unselected population) were considered as with low risk of bias); high risk of bias represents studies with higher risk of selecting participants with higher probability of having GDM (e.g. laboratory databases, hospital-based studies)
[4] Although some study centers would have a higher probability of including women with greater risk for diabetes, we considered the overall risk of selection bias as low for the HAPO study.
[5] Probably plasma glucose

Supplementary table 3: Prevalence (%) of GDM according to different criteria and proportion of IADPSG-GDM women with glucose abnormal for each cut-off

Study	N	GDM IADPSG	GDM 1999 WHO[1]	GDM former-ADA	GDM ADIPS	FPG ≥ 92 (%)	1h-PG ≥180 (%)	2h-PG ≥153 (%)
Corrado 2012 – Italy	738	11.9	-	-	-	-	-	-
Hirst 2012 – Vietnam	2772	20.4	24.3	5.9	20.8	-	-	-
Agarwal 2012 – UAE	849	32.9	18.4	13.3	20.3	-	-	-
Agarwal 2010 – UAE	10283	37.7	-	12.9	-	76.8	-	-
Black 2012 - USA Florida	10459	24.1	-	-	-	-	-	-
Dahanayaka 2012 - Sri Lanka	405	8.9	7.2	-	-	72.2	38.9	36.1
HAPO 2008 – Bellflower, USA	1981	25.5	-	-	-	73.3	48.9	27.1
HAPO 2008 - Singapore	1787	25.1	-	-	-	47.2	65.0	46.8
HAPO 2008 – Cleveland, USA	797	25.0	-	-	-	63.8	48.2	37.7
HAPO 2008 - Manchester, UK	2376	24.3	-	-	-	66.8	56.9	34.9
HAPO 2008 – Thailand	2499	23.0	-	-	-	24.0	75.8	43.3
HAPO 2008 – Chicago, USA	753	17.3	-	-	-	53.1	46.2	46.2
HAPO 2008 – Belfast, UK	1671	17.1	-	-	-	62.6	45.8	24.8
HAPO 2008 – Toronto, Canada	2028	15.5	-	-	-	66.2	48.1	33.8
HAPO 2008 – Providence, USA	757	15.5	-	-	-	72.6	38.5	34.2
HAPO 2008 – Newcastle, AU	668	15.3	-	-	-	63.7	47.1	37.3
HAPO 2008 - Hong Kong, China	1654	14.4	-	-	-	26.1	61.8	65.1
HAPO 2008 - Brisbaine, AU	1444	12.4	-	-	-	50.3	47.5	39.1
HAPO 2008 - Barbados	2093	11.9	-	-	-	73.9	32.1	43.0
HAPO 2008 - Petah-Tiqva, Israel	1818	10.1	-	-	-	42.9	62.0	33.2
HAPO 2008 – Beersheba, Israel	1631	9.3	-	-	-	57.2	40.8	25.7
O'Sullivan 2011 - Ireland	5500	12.4	9.5	-	-	57.9	57.9	50.3
Huynh 2011 – Melbourne, AU	5473	18.7	-	-	14.0	51.2	-	-
Karatodorova 2010 - Bulgaria	299	34.4	16.7	9.7	-	88.3	23.3	19.4
Kun 2013 – Hungary	1080	16.4	7.5	-	-	-	-	-
Lacaria 2013 – Italy	2274	18.9	-	-	-	-	-	-
Moses 2011 – Wollongong, AU	1275	13.0	-	-	9.6	57.2		
Savona-Ventura 2012 – Mediteranean region	1368	26.6	21.2[2]	8.7	-			
EBDG 2001 – Brazil	4998	18.3	7.6	2.8	-	83.3		

N: number of participants; GDM: gestational diabetes mellitus, IADPSG: International Association of Diabetes and Pregnancy Study Groups; WHO: World Health Association; ADA: American Diabetes Association; ADIPS: Australian Diabetes in Pregnancy Society; FPG: fasting plasma glucose; PG: plasma glucose; UAE: United Arab Emirates; NR: not reported; AU: Australia; USA: United States of America; UK: United Kingdom.

[1] FPG criterion varies for 1999 WHO criteria. Hirst 2012, EBDG 2001, Karatadova 2010, Agarwall 2012 and Dahanayaka 2012 considered FPG≥126mg/dL (≥7.0mmol/dL) as threshold; O'Sullivan 2011 considered FPG≥110mg/dL (≥6.1mmol/dL) as threshold. FPG was not considered in the HAPO study for estimate the prevalence according to the 1999 WHO criteria; Kun 2013 and Savona-Ventura 2012 does not describe the threshold considered.
[2] Partial sample (n=1210)

Supplementary table 4: Prevalence of GDM according to different criteria and proportion GDM women with glucose impaired for each cut-off, according to modified-IADPSG criteria

Study	N	GDM (%) modified-IADPSG	GDM 1999 WHO	GDM former-ADA	GDM ADIPS	FBG ≥ 92 (%)	1h-BG ≥180 (%)	2h-BG ≥153 (%)
Bachaoui 2011 - Algeria	1680	19.6	9.3	-	-	-	NA	-
Jenum 2012 - Norway	759	31.5	13	-	-	89.5	NA	23
Kun 2011 – Hungary	1835	16.6	8.7	-	-	-	NA	-
Richardson 2011 - UK	1070	17.5	11.7	-	-	-	NA	-

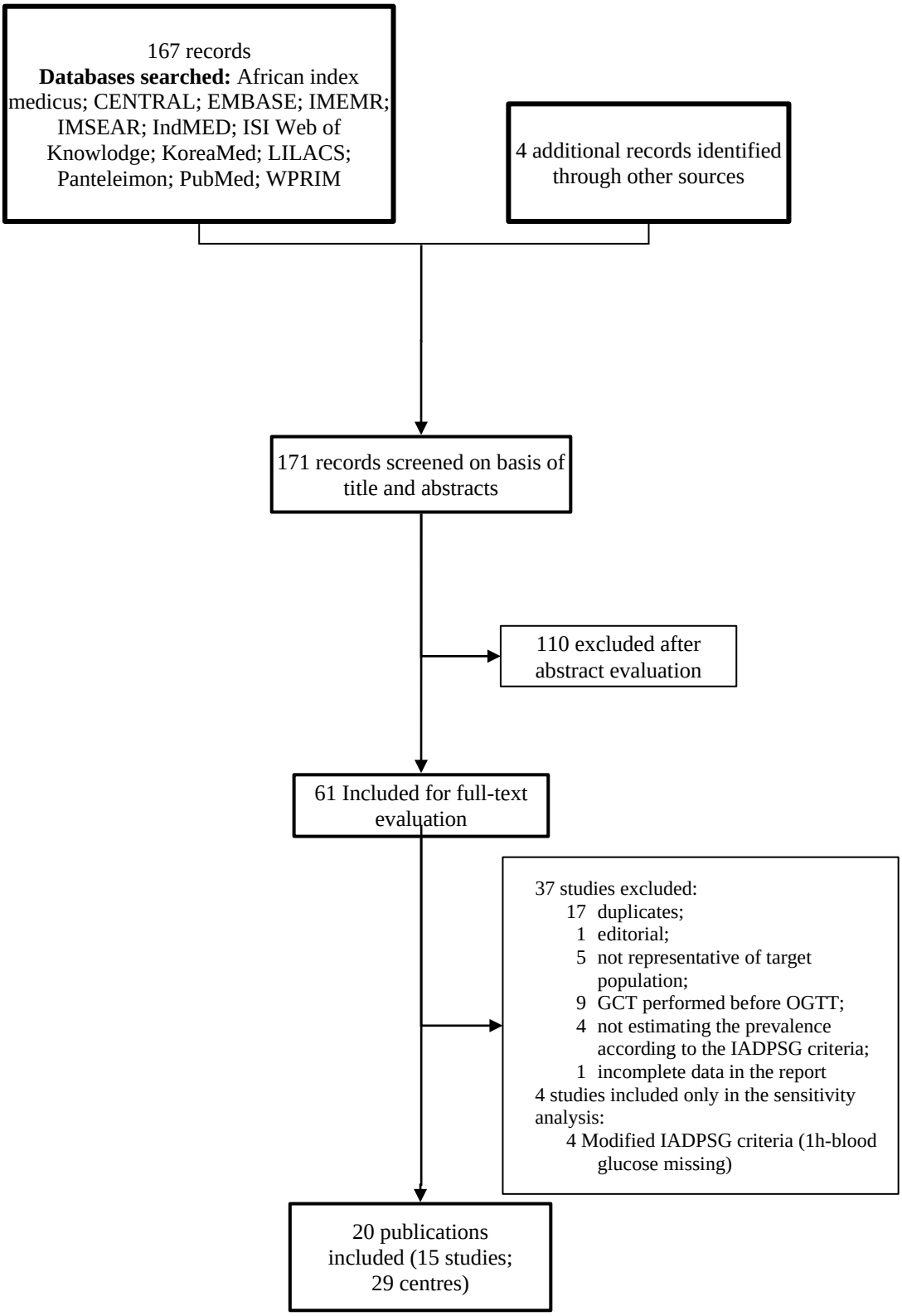
N: number of participants; GDM: gestational diabetes mellitus, IADPSG: International Association of Diabetes and Pregnancy Study Groups; WHO: World Health Association; ADA: American Diabetes Association; ADIPS: Australian Diabetes in Pregnancy Society; FPG: fasting plasma glucose; PG: plasma glucose; NA: not applicable; UK: United Kingdom.

Supplementary table 5: Proportion of GDM pregnancies with abnormal results for each cut-off value (according to the IADPSG criteria)

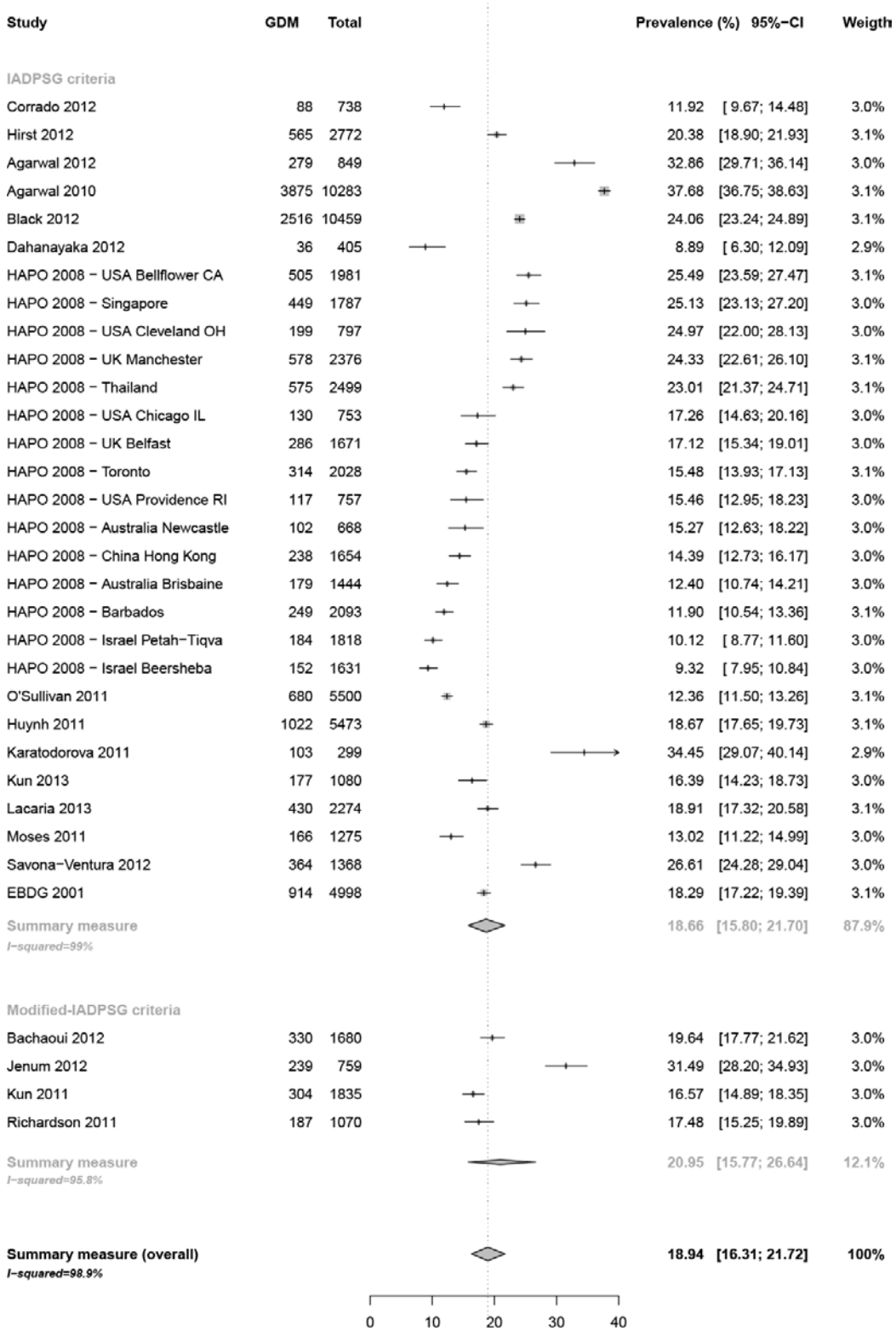
Cut-off value	Number of studies	Number of women with GDM	Proportion of GDM women with abnormal glucose value
FPG ≥ 92 mg/dL	22	11053	60.8% (95% CI 53.1 – 68.3)
1h-PG ≥ 180 mg/dL	18	5076	49.6% (95% CI 43.6 – 55.7)
2h-PG ≥ 153 mg/dL	18	5076	37.6% (95% CI 32.7 – 43.7)

GDM: gestational diabetes mellitus; IADPSG: International Association of Diabetes in Pregnancy Study Groups; FPG: fasting plasma glucose; PG: plasma glucose

Supplementary figure 1. Flow diagram of literature search and study selection

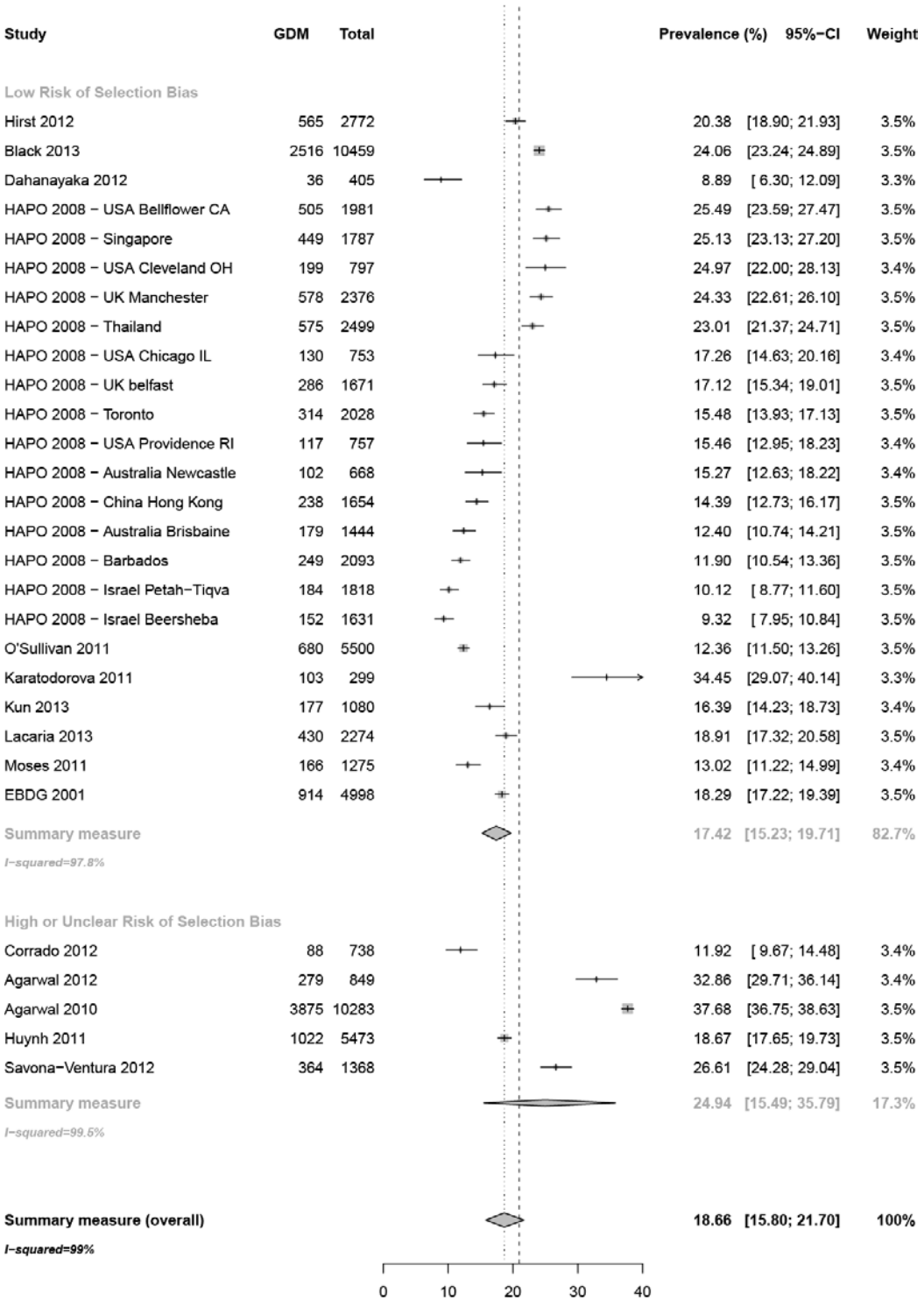


Supplementary figure 2: Sensitivity analysis – prevalence of gestational diabetes mellitus including studies with modified IAPDSG criteria



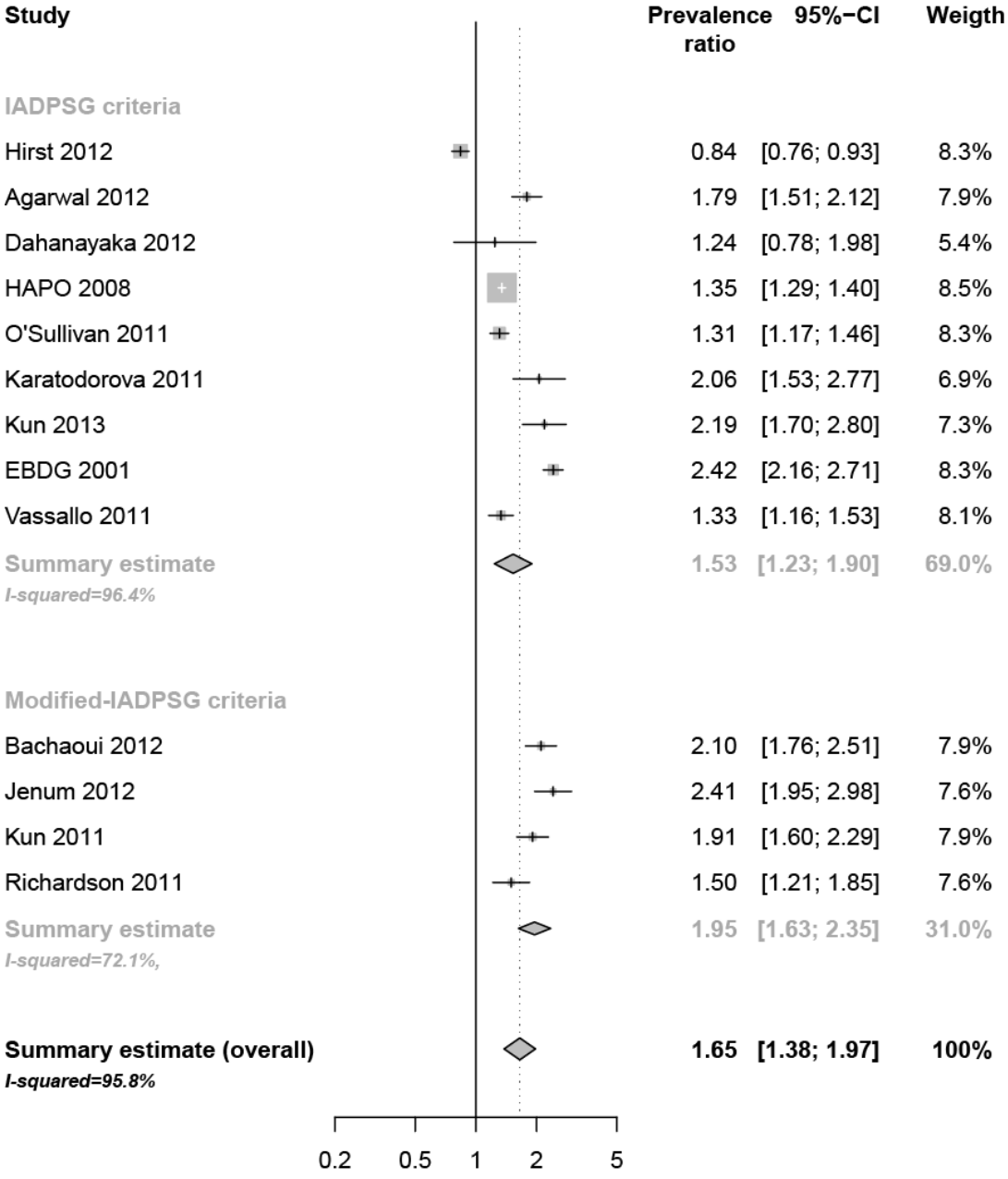
GDM: gestational diabetes mellitus; CI: confidence interval; IADPSG: International Association of Diabetes in Pregnancy; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois; UK: United Kingdom

Supplementary figure 3: Sensitivity analysis – prevalence of gestational diabetes mellitus according to the risk of selection bias



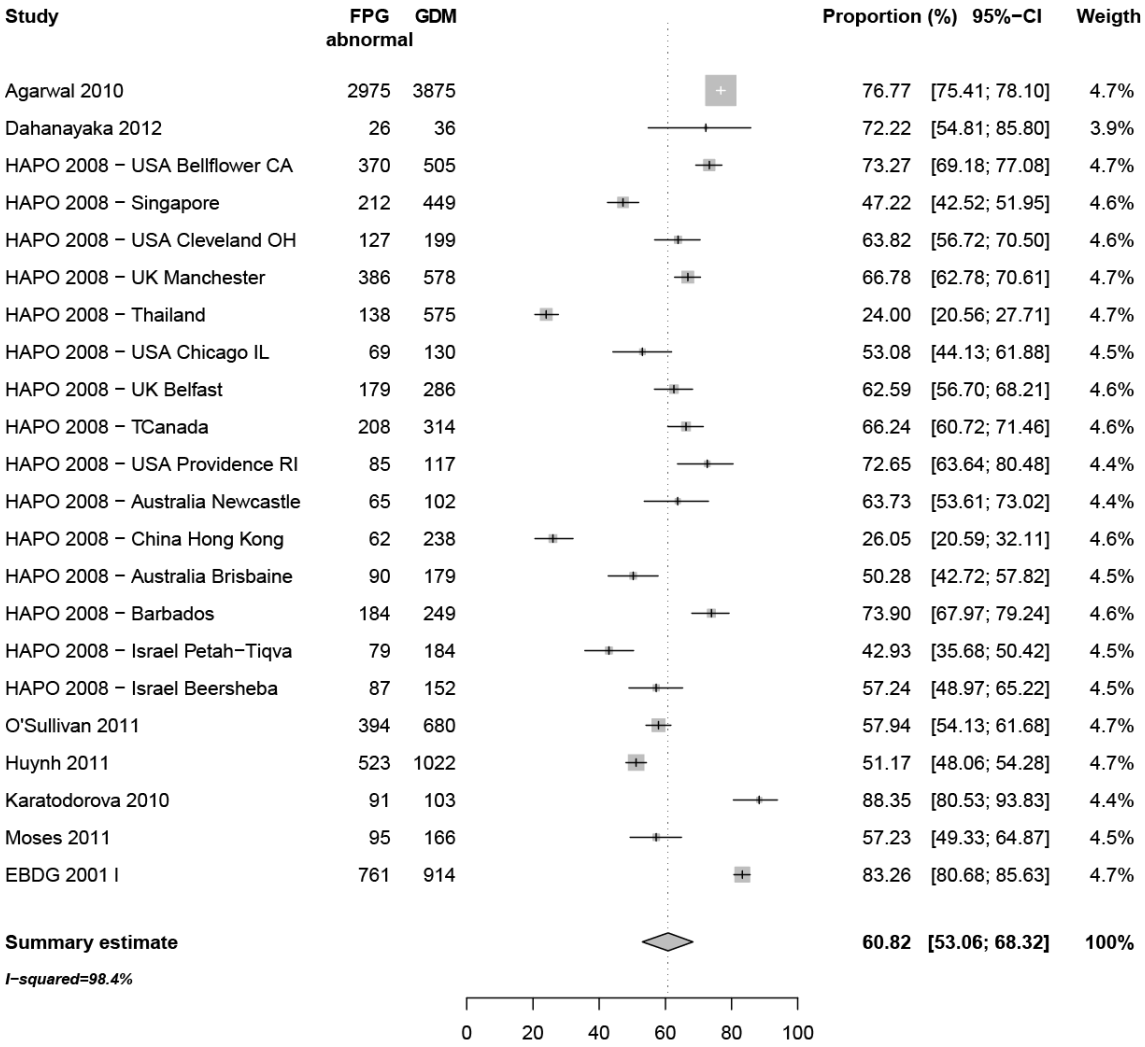
GDM: gestational diabetes mellitus; CI: confidence interval; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois; UK: United Kingdom

Supplementary figure 4: Sensitivity analysis – prevalence increase of gestational diabetes mellitus with the IADPSG criteria compared to the 1999 WHO, including studies with modified IADPSG criteria



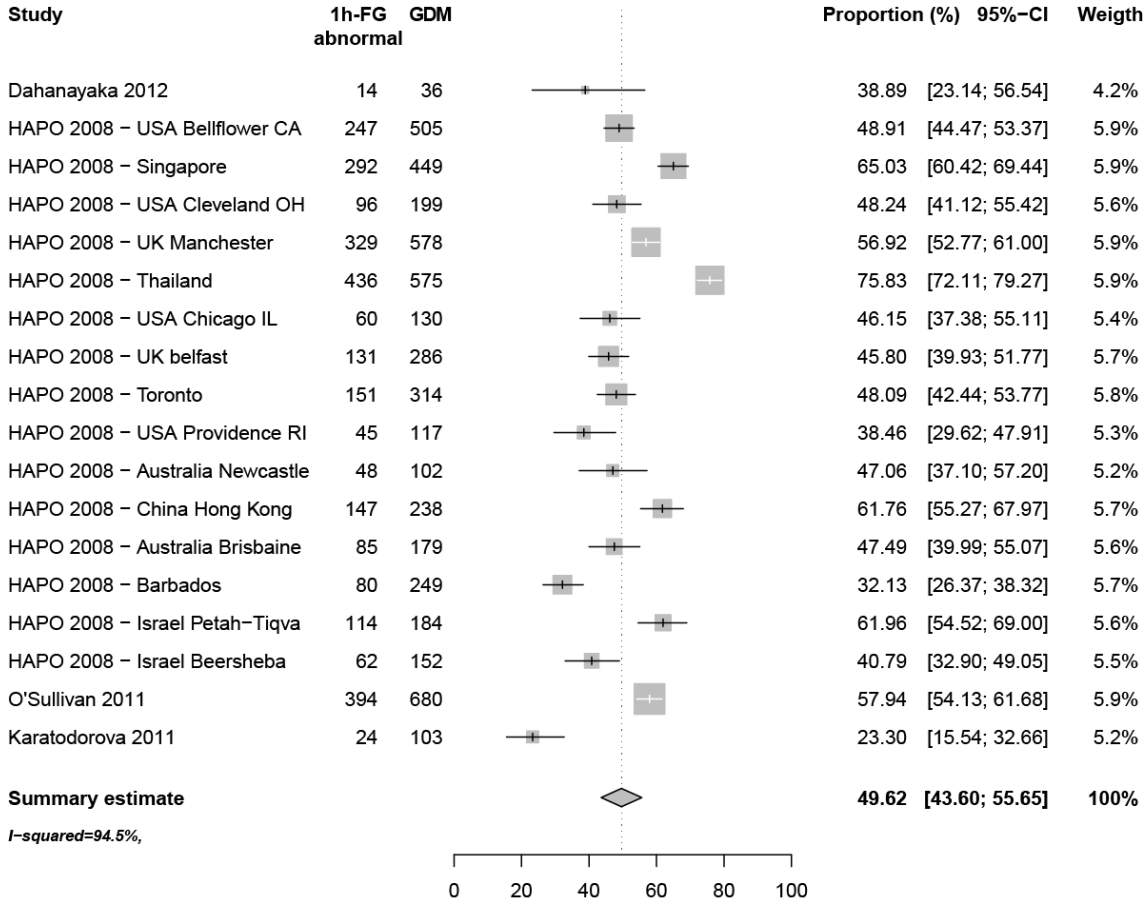
IADPSG: International Association of Diabetes in Pregnancy; WHO: World Health Organization

Supplementary figure 5: Proportion of pregnancies with gestational diabetes mellitus according to the IADPSG criteria presenting abnormal fasting plasma glucose (>=92mg/dL)



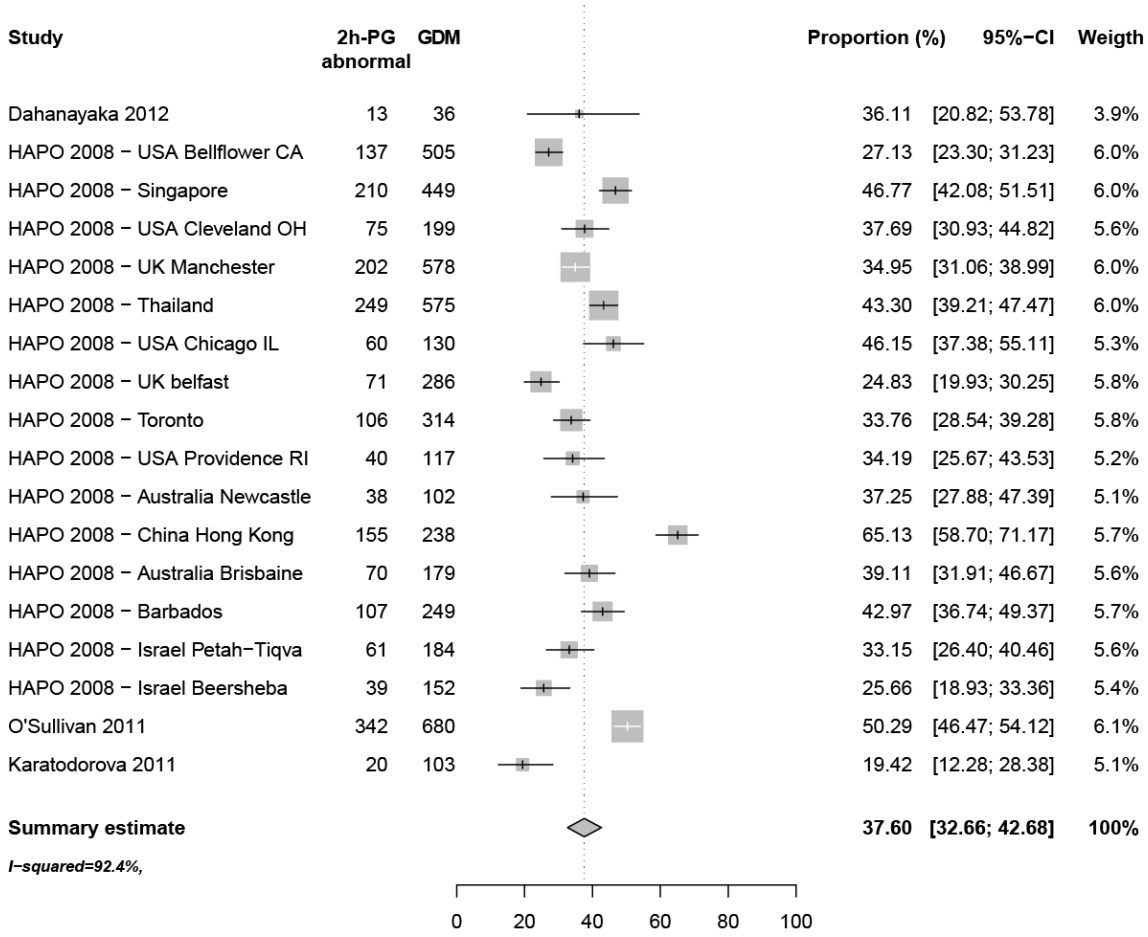
GDM: gestational diabetes mellitus; FPG: fasting plasma glucose; CI: confidence interval; IADPSG: International Association of Diabetes in Pregnancy; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois; UK: United Kingdom

Supplementary figure 6: Proportion of pregnancies with gestational diabetes mellitus according to the IADPSG criteria presenting abnormal1h-plasma glucose (>=180mg/dL)



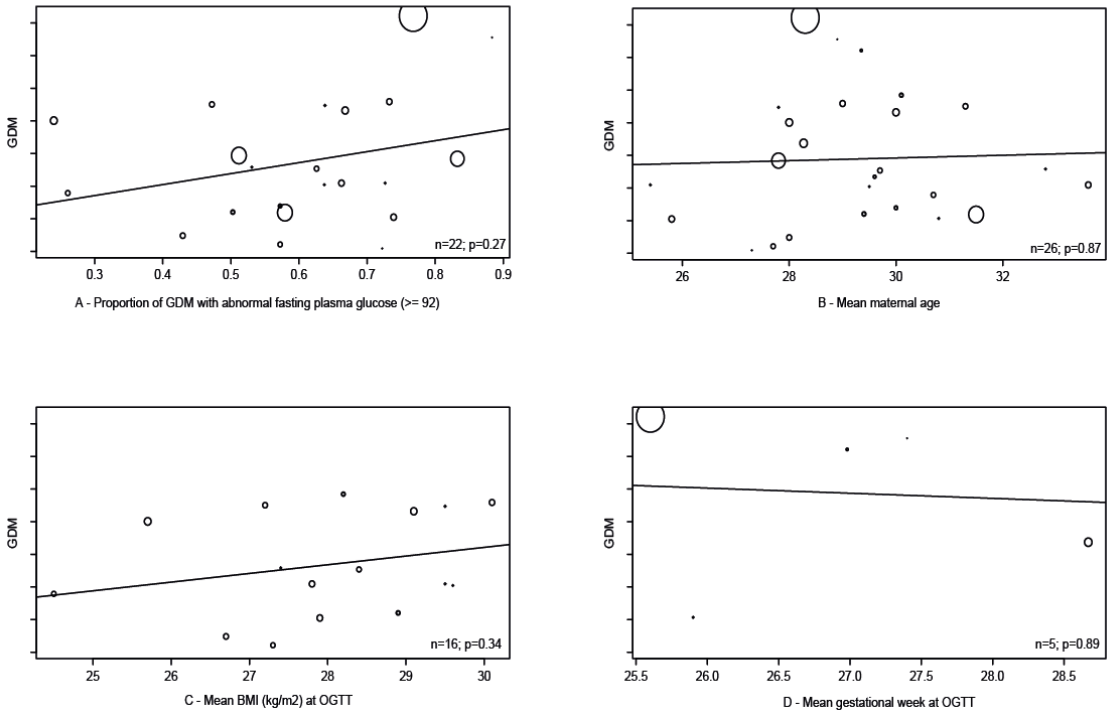
GDM: gestational diabetes mellitus; PG: plasma glucose; CI: confidence interval; IADPSG: International Association of Diabetes in Pregnancy; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois; UK: United Kingdom

Supplementary figure 7: Proportion of pregnancies with gestational diabetes mellitus according to the IADPSG criteria presenting abnormal 1h-plasma glucose (>=153mg/dL)



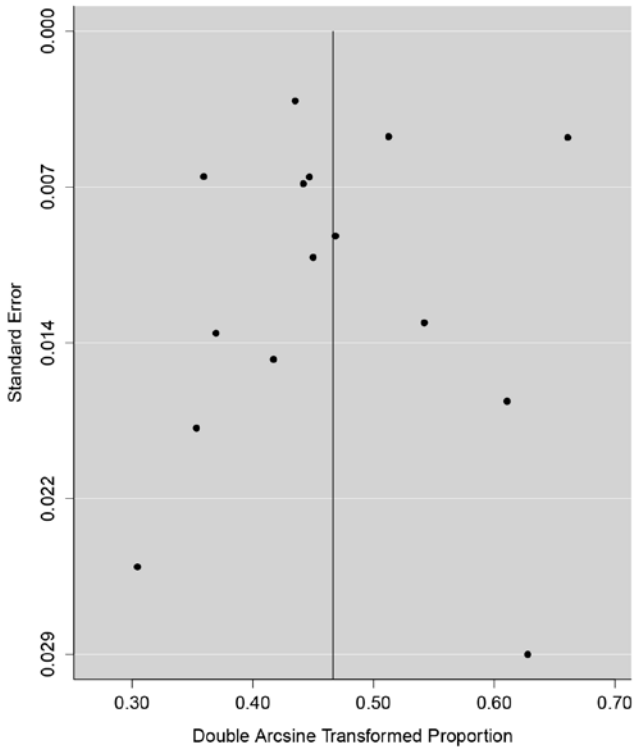
GDM: gestational diabetes mellitus; PG: plasma glucose; CI: confidence interval; IADPSG: International Association of Diabetes in Pregnancy; CA: California; OH: Ohio; RI: Rohde Island; IL: Illinois; UK: United Kingdom

Supplementary figure 8: Sensitivity analysis - meta-regression of the association of GDM prevalence and study's factors (proportion of women with impaired fasting plasma glucose, mean maternal age, mean BMI at OGTT and mean gestational age at OGTT)

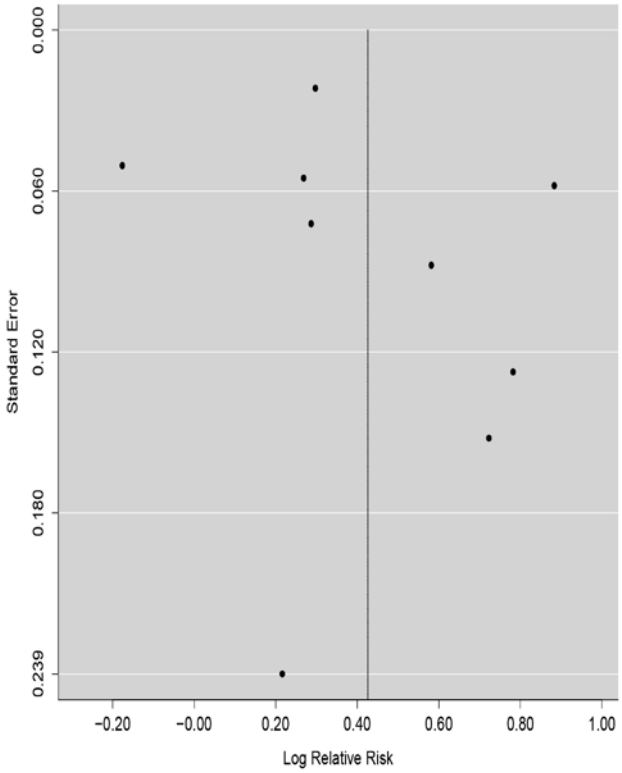


GDM: gestational diabetes mellitus; n: number of studies; BMI: body mass index; OGTT: oral glucose tolerance test

Supplementary figure 9: Assessment of publication bias – funnel plot for the prevalence of gestational diabetes mellitus



Supplementary figure 10: Assessment of publication bias – funnel plot for the Prevalence increase of Gestational Diabetes Mellitus with the IADPSG criteria compared to the 1999 WHO



Appendix 1 – Search strategy

#1: "international association of diabetes in pregnancy study groups"
#2: "international association of diabetes in pregnancy study group"
#3: IADPSG
#4: #1 OR #2 OR #3

Appendix 2: List of studies with modified IADPSG criteria included in the sensitivity analysis.

Study	Reason for exclusion
11 - Bachaoui 2012	No data available for 1h-PG
69 - Jenum 2012	No data available for 1h-PG
81 - Kun 2011	No data available for 1h-PG
137 - Richardson 2011	No data available for 1h-PG

PG – Plasma glucose

Appendix 3 - List of excluded studies

Study	Reason for exclusion
4 - Agarwal 2012	Two-steps approach: OGTT after GCT
10 - Avalos 2012	Duplicate data
12 - Balaji 2012	Provides prevalence only according to fasting plasma glucose
14 - Benhalima 2011	Two-steps approach: OGTT after GCT
16 - Benhalima 2012	Two-steps approach: OGTT after GCT
17 – Black 2012	Duplicate data
18 – Black 2010	Duplicate data
21 – Blatt 2011	Two-steps approach: OGTT after GCT
22 - Bodmer-Roy 2012	Two-steps approach: OGTT after GCT
76 - Boyadzhieva 2011	Not representative of general population
36 - Dahanayaka 2012	Duplicate data
37 – Dar 2012	Incomplete data to estimate the prevalence
42 – Disse 2012	Only pregnancies positives according to the 1999 WHO criteria
44 – Edwards 2012	Not representative of general population
54 – Gobi 2012	Not representative of general population
58 - Hadden 2010	Duplicate data
61 - Healy 2012	Duplicate data
62 - Healy 2012b	Duplicate data
64 - Hirst 2012	Duplicate data
66 - Holt 2011	Editorial
70 - Kalter-Leibovici 2012	Duplicate data
74 - Karamanos 2012	Duplicate data
78 - Khan 2012	Only estimate the prevalence of FPG above 92mg/dL
87 - Lapolla 2010	Duplicate data
88 - Lapolla 2011	Reclassification of women with previous diagnosis of GDM
110 - Morikawa 2010	Two-steps approach: OGTT after GCT
111 - Morkrid 2011	Duplicate data
114 - Morkrid 2012	Duplicate data
117 - Munigoti 2011	Not representative of general population
128 - O'Sullivan 2012	Duplicate data
134 - Resi 2012	Duplicate data
136 - Reyes-Munoz 2012	Two-steps approach: OGTT after GCT
145 - Siyani 2011	Not representative of general population
147 - Sommer 2012	Duplicate data
144 - Sivappriyan 2012	Two-steps approach: OGTT after GCT
152 - Tran 2012	Duplicate data
159 – Wei 2011	Two-steps approach: OGTT after GCT

OGTT: oral glucose tolerance test; GCT: glucose chalange test; WHO: World Health Organization; FPG: fasting plasma glucose; GDM: gestational diabetes mellitus

9. CONCLUSÕES E CONSIDERAÇÕES FINAIS

O diabetes mellitus gestacional (DMG) é uma complicação frequente da gestação, associada a uma gama de eventos adversos materno-fetais.

Evidências consistentes apontam para benefícios importantes do tratamento específico para o DMG, como a redução em cerca de 30 a 50% da incidência de macrossomia, nascidos grande para a idade gestacional, pré-eclampsia e distócia de ombro.(Falavigna 2012)

No entanto, como o GDM não produz sintomas, seu diagnóstico requer rastreamento sistemático na gestação e não há estudos prospectivos adequados que avaliem o impacto de tal rastreamento. Evidências indiretas apontam benefícios advindos do rastreamento universal com os critérios diagnósticos da Organização Mundial de Saúde (OMS) de 1999 e da *International Association of Diabetes and Pregnancy Study Group* (IADPSG). Contudo o impacto populacional do rastreamento na redução de complicações é pequeno, uma vez que eventos adversos como pré-eclampsia e nascidos grandes para a idade gestacional são comuns em gestações normais.(Falavigna 2013) O rastreamento baseado no critério da IADPSG parece prevenir mais eventos adversos da gravidez, possivelmente porque classifica como diabetes gestacional um número maior de mulheres. Não está claro se o benefício do tratamento será o mesmo para esses casos adicionais. Além disso, o maior número de mulheres com diabetes gestacional que requer tratamento promove aumento dos custos e do uso das estruturas de serviços de saúde.

É importante também considerar o impacto da adoção do novo critério da IADPSG no SUS. A estimativa para a prevalência do DMG, globalmente, é de 18,7%; no Brasil, reanálise do Estudo Brasileiro do Diabetes Gestacional encontrou prevalência de 18,3% aplicando o critério diagnóstico da IADPSG, um aumento superior a 120% quando

comparado ao critério da OMS de 1999.(Campos 2011) Essa prevalência de 18,3% provavelmente subestima a prevalência atual esperada com o novo critério, pois ela parte de dados gerados na década de 1990, quando a epidemia de obesidade não estava tão alastrada no Brasil.

Uma limitação desta tese é a falta de dados sobre custo-efetividade do rastreamento. Até o presente momento, três estudos de custo-utilidade avaliaram o rastreamento universal baseado no critério diagnóstico da IADPSG. (Mission 2012, Werner 2012, Marseille 2013) Em geral, a adoção do novo critério é custo-efetiva somente quando se considera a prevenção materna do diabetes mellitus tipo 2. A variabilidade populacional da prevalência do DMG e as diferenças nos custos e na estrutura dos sistemas de saúde apontam a importância de análises econômicas com dados locais para melhor subsidiar a implementação do novo critério de rastreamento.

Finalmente, são necessários ainda alguns desenvolvimentos metodológicos na abordagem do GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) para a avaliação da qualidade da evidência relacionada a questões de prevalência e a questões de acurácia prognóstica. A experiência aqui desenvolvida permitirá, como trabalho posterior à tese, que esses desenvolvimentos sejam traduzidos em artigos para publicação com demais membros do grupo GRADE.

10. REFERÊNCIAS BIBLIOGRÁFICAS ADICIONAIS

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