Universidade de Brasília

Faculdade de Ciências da Saúde

Programa de Pós-Graduação em Nutrição Humana

Prevalência Mundial da Ingestão Insuficiente de Iodo em Gestantes: Revisão Sistemática e Metanálise

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Dissertação apresentada ao Programa de Pós-graduação em Nutrição Humana, Universidade de Brasília, para obtenção do título de Mestre em Nutrição Humana, área de concentração Nutrição e Saúde – dos indivíduos às coletividades.

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Dedicatória

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RESUMO

Introdução: A ingestão insuficiente de iodo durante a gestação está associada a agravos na saúde materno-infantil. Por esse motivo, a identificação de dados sobre a prevalência de consumo insuficiente de iodo em gestantes de diferentes países pode auxiliar no melhor controle clínico-nutricional deste grupo e também na reformulação de políticas públicas focadas na erradicação da deficiência de iodo em gestantes e seus agravos. **Objetivo:** Estimar a prevalência da ingestão insuficiente de iodo em gestantes em diferentes regiões do mundo. **Métodos:** Esta revisão sistemática foi realizada seguindo as diretrizes do *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols* (PRISMA-P). Os artigos foram pesquisados nas seguintes bases de dados: Medline (PubMed), Embase, Scopus, Web of Science, Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs). A literatura cinzenta foi consultada por meio do Google Scholar e do ProQuest Dissertations & Theses Global. Não foram restringidos idiomas e tempo de publicação. A seleção dos estudos e a extração dos dados foram conduzidas por duas avaliadoras de maneira independente. O risco de viés foi analisado segundo instrumento específico recomendado pelo *Joanna Briggs Institute*, seguindo nove critérios relacionados à amostragem, ao método de mensuração do desfecho, à análise estatística e à taxa de resposta. Calculou-se a metanálise com modelo de efeitos aleatórios e foram realizadas meta-regressão, análise de subgrupos e análise do viés de publicação. A análise dos dados foi realizada no pacote estatístico STATA® versão 15. **Resultados:** Foram identificados 4.443 artigos, dos quais 58 foram incluídos e reportaram a avaliação de 160.889 gestantes. A prevalência da ingestão insuficiente de iodo foi 53% (IC 95% 46–59; I^2=99.8%) quando sumarizada a medida de todos os estudos com dados disponíveis no mundo. Gestantes que vivem em países considerados como regiões insuficientes em iodo apresentaram prevalência maior de ingestão insuficiente (82%; IC 95%: 70–94; I^2 = 97,7%) quando comparado a países considerados como regiões suficiente (51%; IC de 95%: 44-57; I^2 = 99,8%). A análise de subgrupos e a meta-regressão não identificaram as causas da heterogeneidade. **Conclusão:** O resultado do presente trabalho permitiu observar a prevalência mundial de ingestão insuficiente de iodo em 53% em gestantes. Apesar do progresso nas políticas de fortificação de iodo e no monitoramento periódico do estado nutricional de

iodo da população em diferentes países, a iodação do sal por si só pode não ser suficiente para garantir a ingestão adequada de iodo entre gestantes.
Palavras-chave: Gravidez; Insuficiência de iodo; Prevalência

ABSTRACT

Introduction: Insufficient iodine intake during pregnancy is associated with worsening maternal and child health. For this reason, the identification of data on the prevalence of insufficient iodine consumption in pregnant women from different countries can assist in the better clinical and nutritional control of this group and also in the reformulation of public policies focused on the eradication of iodine deficiency in pregnant women and their health problems. **Objective:** To estimate the prevalence of insufficient iodine intake in pregnant women from different regions of the world. **Methods:** This systematic review was carried out following the guidelines of the *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).* The articles were searched in the following databases: Medline (PubMed), Embase, Scopus, Web of Science, Scientific and Technical Literature of Latin America and the Caribbean (Lilacs). Gray literature was consulted through Google Scholar and ProQuest Dissertations & Theses Global. Languages and publication time were not restricted. The selection of studies and data extraction were conducted by two evaluators independently. The risk of bias was analyzed according to a specific instrument recommended by the *Joanna Briggs Institute,* following nine criteria related to sampling, the method of measuring the outcome, the statistical analysis, and the response rate. The meta-analysis was calculated using a random effects model and meta-regression, subgroup analysis and publication bias analysis were performed. Data analysis was performed using the STATA® version 15 statistical package. **Results:** 4,443 articles were identified, of which 58 were included and reported the evaluation of 160,889 pregnant women. The prevalence of insufficient iodine intake was 53% (95% CI 46–59; I^2 = 99.8%) when summarizing the measurement from all studies with data available worldwide. Pregnant women living in countries considered part of regions with insufficient iodine had a higher prevalence of insufficient intake (82%; 95% CI: 70–94; I^2 = 97.7%) when compared to countries considered as sufficient regions (51%; CI 95%: 44-57; I^2 = 99.8%). Subgroup analysis and meta-regression did not identify the causes of heterogeneity. **Conclusion:** The result of the present study allowed us to observe the worldwide prevalence of insufficient iodine intake in 53% in pregnant women. Despite progress in iodine fortification policies and periodic monitoring of the iodine nutritional status of the population in different countries, salt iodination alone may not be sufficient to ensure adequate iodine intake among pregnant women.

Keywords: Pregnancy; Iodine insufficiency; Prevalence

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Lista de Abreviaturas

ANVISA - Agência Nacional de Vigilância Sanitária

DIT – Diiodotirosina

hCG - Gonadotrofina Coriônica Humana

HT - Hormônios tireoidianos

IC 95% - Intervalo de Confiança de 95%

ICCIDD - Conselho Internacional para Controle dos Distúrbios por Deficiência de Iodo

IDD - Distúrbios por Deficiência de Iodo

IG – Idade gestacional

LILACS - Literatura Latino-Americana e do Caribe em Ciências da Saúde

MIT - Hormônio Monoiodotirosina

NIS - Proteína transportadora de membrana dependente do gradiente de sódio

OMS - Organização Mundial da Saúde

PRESS - Peer Review of Electronic Search Strategies

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO - Prospective Register of Systematic Reviews

T3 - Triiodotironina

T4 – Tiroxina

Tg - Tireoglobulina

TPO - Tireoperoxidase

TRH - Tirotrofina

TSH - Hormônio estimulante da tireoide

UIC - Concentração de iodo urinário

UNICEF - Fundo das Nações Unidas para a Infância

µg – Microgramas

1. Introdução

O período gestacional está associado a mudanças fisiológicas significativas no organismo, decorrente de uma hiper estimulação dos sistemas cardiovascular, renal, pulmonar e endócrino (VELASCO, BATH & RAYMAN, 2018). A funcionalidade da glândula tireoide também é afetada, sendo que na primeira metade do período gestacional, ocorre estimulação direta da tireoide por níveis elevados de gonadotrofina coriônica humana (hCG) produzida pela placenta, que se assemelha estruturalmente ao hormônio estimulante da tireoide (TSH) (SPRINGER et al, 2017). Durante esse período, a tireoide fetal ainda está inativa e depende totalmente do fornecimento materno do hormônio tiroxina, também chamado de tetraiodotironina (T4) dos quais a produção e o metabolismo são dependentes dos oligoelementos iodo e selênio (VELASCO, BATH & RAYMAN, 2018).

O iodo é um micronutriente essencial que tem participação na síntese dos hormônios da tireoide e é especialmente importante durante a gravidez e no início da vida, devido ao seu papel no desenvolvimento do sistema nervoso. Apesar da glândula tireoide do feto começar a funcionar aproximadamente entre a 18ª e 20ª semana de gestação, o suprimento de iodo necessário para seu funcionamento continua vindo da mãe (PEARCE et al, 2016). Na gestação, a demanda de iodo materna aumenta em decorrência das mudanças fisiológicas e do aumento da filtração glomerular nessa fase levando à maior excreção urinária. Esta excreção também chamada de iodúria, é um marcador bioquímico que possibilita avaliar o estado nutricional de iodo populacional e reflete alterações recentes nos níveis de ingestão (SOUZA et al, 2015; VELASCO, BATH & RAYMAN, 2018).

A deficiência grave de iodo durante a gestação aumenta o risco de aborto e da mortalidade infantil resultando ainda, em hipotireoidismo fetal e efeitos adversos sérios associados à saúde, sendo eles o cretinismo e o retardo de crescimento (PEARCE et al, 2016). Uma vez que, o hormônio tireoidiano desempenha um papel essencial na migração neuronal, mielinização, transmissão sináptica e plasticidade, existe uma possível associação entre a disfunção tireoidiana em gestantes e dano neurológico, incluindo deficiência intelectual na criança (VELASCO et al, 2009).

Apesar do progresso na erradicação da deficiência de iodo em muitos países por meio do uso de sal iodado como estratégia de saúde pública, a deficiência de iodo continua sendo uma questão a ser tratada em gestantes em todo o mundo (SOUZA et al, 2015). As mulheres que vivem em regiões suficientes de iodo normalmente iniciam a gestação com estoques intratireoidianos adequados sendo capazes de atender as demandas dessa fase, desde que mantenham o consumo adequado de iodo. Já as mulheres que residem em regiões insuficientes de iodo, podem começar a gestação com reservas inadequadas deste nutriente intratireoidiano, sendo rapidamente esgotadas durante o período (PEARCE, 2012).

Uma revisão sistemática mostrou estudos que indicavam a variação da prevalência de deficiência iódica em gestantes no mundo entre 16,1% a 84,0% (CANDIDO et al, 2019). Apesar da apresentação do dado de prevalência mundial, esta revisão limitou a análise em gestantes adultas, não apresentou meta-análise dos resultados e restringiu a busca em relação aos idiomas, o que pode não refletir a exatidão dos resultados apresentados. Neste contexto torna-se relevante a sumarização dos resultados dos estudos individuais, buscando aprimorar o monitoramento constante do estado nutricional de iodo durante a gestação e auxiliar o combate e controle dos distúrbios por deficiência de iodo no grupo materno infantil, além de colaborar para a reformulação de políticas públicas de saúde voltadas para o combate da inadequação desses distúrbios nessa fase da vida.

2. Referencial teórico

2.1 Aspectos fisiológicos da tireoide

O iodo é um componente essencial com participação conhecida na síntese dos hormônios tireoidianos (HT): triiodotironina (T3) e tiroxina (T4). O estoque corporal de desse nutriente concentra-se em sua maior parte, na glândula tireoide podendo assumir níveis de 70% a 80%. O restante, é distribuído por todo o corpo, principalmente nas glândulas mamárias, salivares e gástricas, além dos rins (ROHNER et al, 2014). O iodo presente nos alimentos é encontrado principalmente na sua forma iônica e reduzido a iodeto no intestino sendo em seguida, absorvido pelo estômago e pelo duodeno, ou ligado a um aminoácido. Todo esse processo de absorção ocorre de forma rápida e praticamente completa (> 90%) (ZIMMERMANN, 2016).

Ao atingir a corrente sanguínea, o iodeto é retirado da circulação, principalmente pela glândula tireoide, por meio de uma proteína transportadora de membrana dependente do gradiente de sódio, denominada em inglês, Na^+/ I^- Symporter (NIS)

(YARRINGTON; PEARCE, 2011). Na tireoide, o iodeto é transportado até a superfície apical do tireócito onde é oxidado pela ação da enzima tireoperoxidase (TPO) e em presença de peróxido de hidrogênio. Em sequência, ele se liga a um aminoácido tirosina selecionado no interior da tireoglobulina (Tg), formando o complexo dos precursores de hormônio monoiodotirosina (MIT) e diiodotirosina (DIT). Uma vez formadas essas iodotirosinas, são então acopladas por uma ligação de éter em uma reação também catalisada pela TPO. O acoplamento de duas moléculas de DIT origina o T4, enquanto a junção de MIT e do DIT resulta no T3 (figura 1).

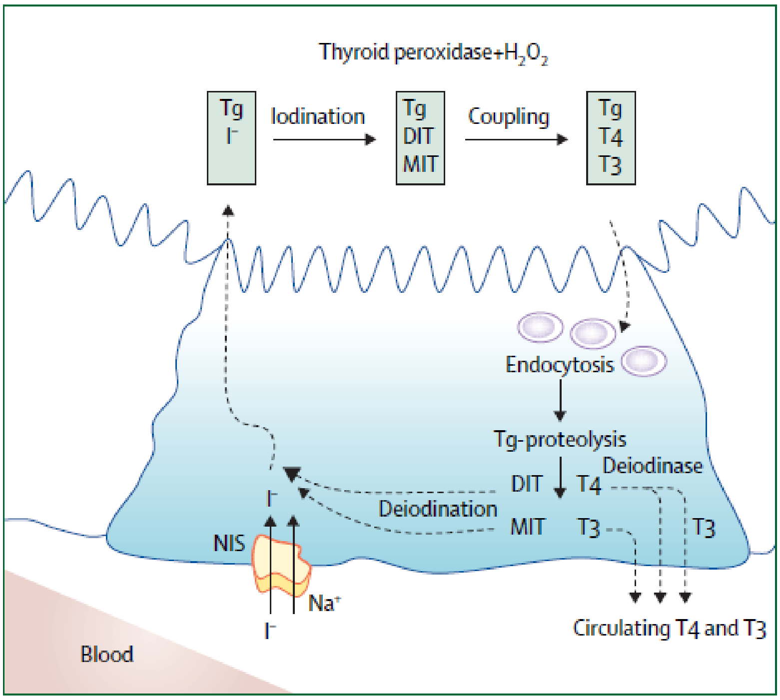

Figura 1 – **Metabolismo do iodo na célula tireoidiana**

Fonte: Zimmermann, (2008).

A forma como o iodo é capturado da circulação para a formação dos hormônios tireoidianos varia de acordo com a produção do hormônio hipotalâmico estimulador de tirotrofina (TRH) e do hormônio estimulador da tireoide (TSH), já que o controle ocorre por *feedback* negativo. Quando há baixo consumo de iodo (<100µg/d), a tireoide adapta-se aumentando a secreção de TSH pela hipófise. Esse aumento de TSH eleva a depuração plasmática de iodeto inorgânico pela tireoide, por meio da estimulação da expressão do NIS (ZIMMERMANN, 2016).

2.2 Adaptações fisiológicas da tireoide na gestação

Na gestação, os níveis elevados de estrógeno determinam mudanças importantes na fisiologia da tireoide. A primeira adaptação que ocorre é o aumento da demanda de iodo dietético na glândula tireoide materna. Essa elevação das necessidades nutricionais é resultante de alguns fatores tais como, o aumento da produção de T4, a transferência de T4 e iodo materno para a manutenção da homeostase fetal e o aumento na taxa de filtração glomerular o que leva à maior depuração e excreção renal de iodeto (YARRINGTON; PEARCE, 2011).

Adicionalmente, no início da gestação ocorre a produção de subunidade alfa da hCG que começa nos primeiros dias de gestação e atinge o pico por volta de 9 a 11 semanas de idade gestacional (IG). Os níveis diminuem até aproximadamente 20 semanas de gestação e permanecem estáveis no período restante da gravidez. O hCG também se liga e estimula o receptor de TSH desencadeando um aumento de aproximadamente 50% na produção de T4. O aumento da produção dos hormônios tireoidianos na gestação requer disponibilidade adequada de iodo (KOREVAAR et al, 2017) (figura 2).

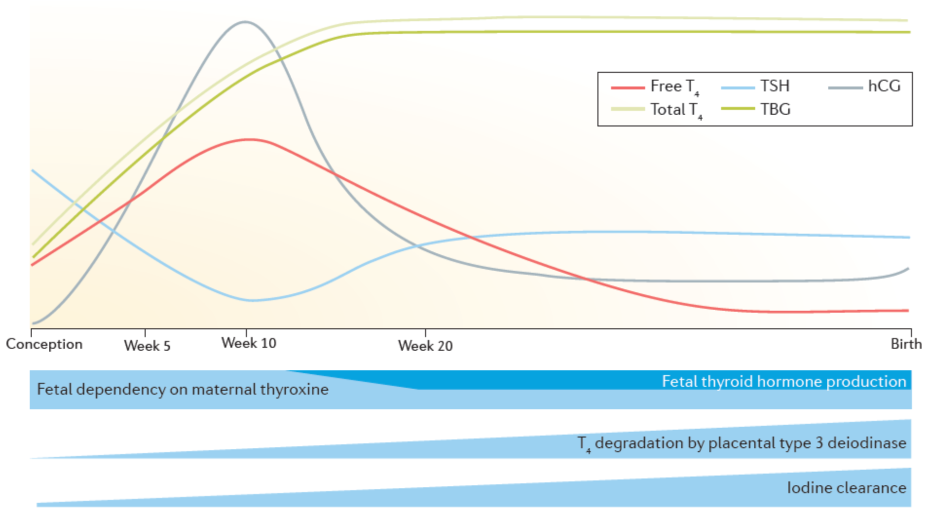

Figura 2 - **Mudanças na fisiologia da tireoide durante a gestação**

Fonte: Korevaar et al, (2017).

Ainda, a produção de hormônios pela tireoide fetal se inicia por volta da vigésima semana gestacional, resultando na dependência exclusiva de T4 e iodo materno que atravessam a placenta para garantir o suprimento das suas necessidades metabólicas no período anterior a essa produção (SAVIN et al, 2003). Outro fator associado a elevação da demanda de iodo materno consiste no aumento da taxa de filtração glomerular para garantir a excreção de iodeto inorgânico plasmático. Como o iodo é excretado passivamente, o aumento da filtração glomerular renal resulta em maiores perdas de iodo ingerido (YARRINGTON; PEARCE, 2011). Para isso, a Organização Mundial da Saúde (OMS), o Fundo das Nações Unidas para a Infância (UNICEF) e o Conselho Internacional para Controle dos Distúrbios por Deficiência de Iodo (ICCIDD) recomendam a ingestão diária de 250 µg de iodo para mulheres grávidas e lactantes, representando um adicional de ingestão em torno de 50 a 100 µg comparado ao valores recomendados para mulheres em idade fértil.

2.3 Deficiência de Iodo

O bócio endêmico foi considerado por um longo tempo como a principal manifestação clínica da deficiência de iodo. Os países frequentemente eram divididos geograficamente em áreas endêmicas e não endêmicas com base na prevalência de bócio. Considerado problema de saúde pública global, os esforços de controle foram direcionados para curar ou reduzir essa manifestação. Com o crescimento da pesquisa clínica e de saúde pública, foi evidenciado que as consequências da deficiência de iodo vão muito além do bócio e dos demais distúrbios da tireoide (ANDERSSON et al, 2005).

Em 1993, reconhecendo a importância da prevenção de Distúrbios por Deficiência de Iodo (DDI), a OMS e a UNICEF recomendaram a iodização universal de sal como a principal estratégia para alcance da eliminação desses distúrbios (ANDERSSON et al, 2005). A deficiência de iodo é uma das principais causas evitável de atraso no desenvolvimento mental na infância e de aumento na mortalidade perinatal. Embora programas de controle da deficiência de iodo, tais como iodização do sal, são eficazes há décadas, a deficiência iódica continua sendo uma grande ameaça para a saúde e desenvolvimento populacional em todo o mundo, principalmente em grupos mais vulneráveis como crianças pré-escolares e gestantes (ANDERSSON et al, 2005).

Alguns fatores podem ter influência na alteração do conteúdo de iodo presente no sal iodado. A distribuição desigual de iodo no sal, em lotes e sacos individuais, devido à mistura insuficiente de sal após o processo de iodização e/ou variação no tamanho de partícula dos cristais de sal em um lote ou saco; a extensa perda de iodo devido a impurezas do sal e condições ambientais durante o armazenamento e distribuição; a perda de iodo devido aos processos de lavagem, cozimento e processamento de alimentos podem alterar a disponibilidade real de iodo no sal iodado (OMS, 2007).

Outros fatores que podem colocar em risco a efetividade dos programas de controle da deficiência iódica são a pobreza e a imigração (ACERVO-GARCIA; ALMEIDA, 2012). O conhecimento sobre a importância do seguimento da gestação por meio dos cuidados pré-natais pode ser particularmente limitado em mulheres com um status socioeconômico ruim ou com barreiras linguísticas ou culturais, que acabam prejudicando seu acesso ao sistema de saúde. Nas sociedades ocidentais, foi demonstrado que a imigração para países estrangeiros subdesenvolvidos pode influenciar o acesso a programas de saúde e paradoxalmente, mulheres que imigram para países com consumo suficiente de iodo também apresentam risco por estarem num novo ambiente que pode favorecer mudanças em seus hábitos alimentares (ACERVO-GARCIA; ALMEIDA, 2012).

2.4 Indicadores do estado nutricional de iodo em gestantes

A avaliação correta do estado nutricional de iodo populacional é necessária para informar as políticas públicas de saúde e a pesquisa clínica sobre nutrição de iodo, o papel da adequação do iodo nos desfechos maternos e neonatais. Existem diferentes métodos de avaliação do status de iodo em gestantes. Entre esses métodos, a concentração de iodo urinário (UIC), também chamada de iodúria é amplamente utilizada em uma amostra representativa. Para essa avaliação em outros grupos populacionais são utilizados indicadores tais como: o tamanho da glândula tireoide mensurado por palpação ou ultrassonografia, a UIC, os níveis séricos de hormônio estimulante da tireoide (TSH), tiroxina total ou livre (T4/T4L), triiodotironina (T3) e de tireoglobulina (Tg) (PEARCE; CALDWELL, 2016).

Aproximadamente 90% do iodo é excretado na urina. Sendo assim, a UIC reflete diretamente a ingestão recente de iodo na dieta e é o indicador mais comum usado em todo o mundo para avaliar o status do iodo. Pode ser expressa de diferentes formatos tais como: excreção de 24-h (µg/d); concentração (µg/kg/L) ou em relação com a excreção de creatinina (µg de iodo/g creatinina) (ROHNER et al, 2014).

Além da avaliação de iodúria ser um indicador prático, usual e aceitável para o cálculo da mediana da UIC, também é utilizada para apresentar a prevalência a deficiência iódica numa população. Porém, esse método não é recomendado para avaliação do status de iodo individual devido a variabilidade diária elevada na ingestão desse micronutriente na dieta (ANDERSEN et al, 2008). A metodologia empregada para análise é validada e amplamente difundida no meio científico. Segundo a OMS (2007), há evidências convincentes de que um perfil de concentrações de iodo da urina de criança ou adulto coletada pela manhã ou de outras amostras obtidas casualmente, fornece uma avaliação adequada do status de iodo de uma população, desde que um número suficiente de amostras ou indivíduos seja investigado não sendo necessário obter amostra de urina de 24h.

Os critérios epidemiológicos internacionais recomendados pela OMS (2007) para a classificação do estado nutricional de iodo para gestantes pela UIC são: Consumo insuficiente se a UIC for < 150 μg/L, adequado (UIC entre 150 e 249 μg/L), acima do recomendado (UIC entre 250 e 499 μg/L) e excessivo (UIC ≥ 500 μg/L).

2.5 Distúrbios por deficiência de iodo na gestação

O hormônio tireoidiano é necessário para a migração neuronal normal e a mielinização do cérebro durante a vida fetal e pós-natal precoce, e a hipotirooxinemia durante esses períodos críticos causa danos cerebral irreversível, com retardo mental e anormalidades neurológicas (PEARCE et al, 2016). A deficiência de iodo tem múltiplas manifestações metabólicas e funcionais que interferem no crescimento e desenvolvimento humano. Essas manifestações surgem quando as necessidades nutricionais de iodo não são supridas e a síntese do hormônio tireoidiano fica prejudicada. Essas manifestações chamadas de DDI estão detalhadas no quadro 1. A forma mais séria de DDI é o cretinismo endêmico, que é um desenvolvimento físico e mental severamente atrofiado permanentemente (OMS, 2007).

Quadro 1 - Distúrbios por deficiência de iodo segundo as fases da vida

Grupos fisiológicos	DDI
Todas as idades	bócio, hipotireoidismo, suscetibilidade aumentada à radiação nuclear.
Fetos	aborto espontâneo, natimorto, anomalias congênitas, mortalidade perinatal.
Neonatos	cretinismo endêmico, incluindo deficiência mental com

	uma mistura de mutismo, diplegia espástica, estrabismo, hipotireoidismo e baixa estatura, mortalidade infantil.
Crianças e adolescentes	função mental prejudicada, desenvolvimento físico retardado, hipertireoidismo induzido por iodo.
Adultos	função mental prejudicada, hipertireoidismo induzido por iodo.

Fonte: OMS (2007).

Durante a gestação, a deficiência grave de iodo aumenta o risco de aborto e da mortalidade infantil resultando ainda, em hipotireoidismo fetal e efeitos adversos sérios associados à saúde do binômio mãe-filho descritos com mais detalhes no quadro 2. Um estudo de coorte realizado na China com 2.087 gestantes, identificou que a insuficiência e o excesso de iodo materno coexistiram durante o início da gravidez e ambos afetaram negativamente o crescimento fetal (CHEN et al, 2018).

Cao et al. (1994), acompanharam crianças desde o nascimento até 3 anos e mulheres em cada trimestre da gestação em uma área de grave deficiência de iodo e cretinismo endêmico na China e observaram que a prevalência de anormalidades neurológicas foi menor em crianças cujas mães receberam suplementação de iodo no primeiro ou segundo trimestre, o quociente de desenvolvimento médio aos 2 anos de idade foi maior nas crianças tratadas com a suplementação de iodo do que aquelas não tratadas e a oferta de suplemento de iodo antes do terceiro trimestre gestacional previu pontuações mais altas nos testes psicomotores das crianças em relação às que forneceram iodo mais tarde na gravidez ou aos 2 anos.

Quadro 2 – Implicações causadas pela deficiência de iodo em cada trimestre gestacional

Trimestre gestacional	DDIs
1º trimestre	aumento do volume da tireoide, aborto espontâneo, diabetes mellitus gestacional, deslocamento placentário precoce, hipertensão, aumento do estresse oxidativo.
2º trimestre	aumento do volume da tireoide, anemia por deficiência de ferro, risco de prematuridade, restrição do crescimento fetal, hipotireoidismo subclínico, pré-eclâmpsia, diarreia, infecção do intestino grosso, infecção de ouvido.

3º trimestre	aumento do volume da tireoide, nódulos na tireoide, redução do superóxido, atividade da dismutase, recém-nascido pequeno para a idade gestacional, eclampsia, baixo peso ao nascer.

Fonte: Candido et al (2020).

2.5 Epidemiologia da deficiência de iodo: prevalência e fatores de risco

Segundo dados da OMS (2007) estima-se que, cerca de 31% da população mundial tenha ingestão insuficiente de iodo, sendo as regiões mais afetadas o sudeste da Ásia e a Europa. Ainda, que aproximadamente 70% das famílias em todo o mundo tenham acesso e usem sal iodado. Apesar do progresso na erradicação da deficiência de iodo em muitos países do mundo por meio do uso de sal iodado como estratégia de saúde pública, a deficiência de iodo continua sendo um problema em gestantes (SOUZA et al, 2015). A figura 3 apresenta o status de iodo global baseado na UIC de crianças em idade escolar.

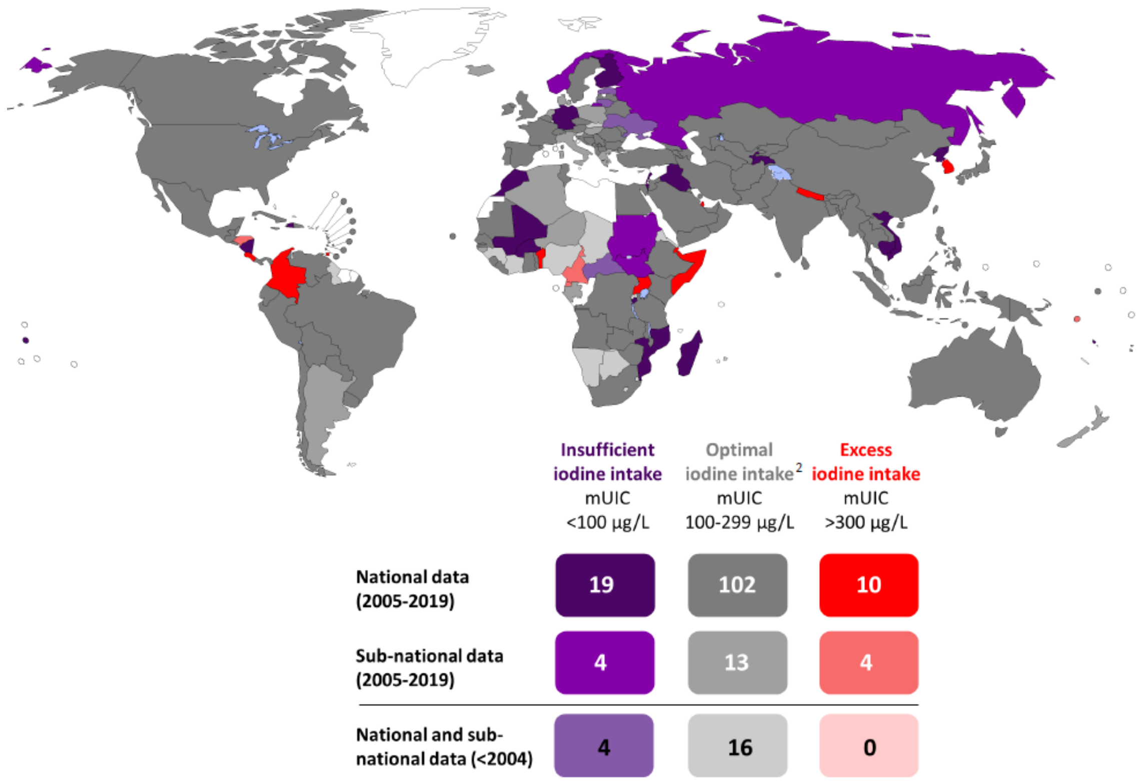

Figura 3 - **Scorecard global de nutrição com iodo em 2020**

Fonte: The Iodine Global Network, (2020).

Bath et al, (2015) recrutaram 230 mulheres primíparas no Reino Unido, entre a 12ª e 14ª semana da gestação e acompanharam-nas em dois momentos distintos sendo eles na 20ª e 35ª semana gestacional respectivamente. A UIC foi medida em amostras de urina local que foram coletadas nas 12ª, 20ª e 35ª semanas e a concentração de creatinina também foi medida para corrigir a diluição da urina. A UIC das amostras de urina coletadas em todos os momentos (n = 662) foi de 56,8 μg/L, e a proporção de iodo/creatinina foi de 116 μg/g, classificando esta coorte como levemente a moderadamente deficiente em iodo.

Em estudo realizado no Irã, região considerada suficiente em iodo foram recrutadas 1072 gestantes de dez províncias nas diferentes partes do país. Foi utilizada a UIC como medida do status de iodo e a mediana estimadas para gestantes foi de 87,3 μg/L, sendo 92,1, 86,0 e 76,8 μg / L, no 1º, 2º e 3º trimestre da gestação, respectivamente. Apesar da suficiência de iodo das crianças em idade escolar no Irã, esses resultados mostram que as mulheres grávidas apresentavam deficiência moderada de iodo (DELSHAD et al, 2016). No Canadá, a iodização universal de sal é obrigatória desde 1920. Numa coorte de gestantes canadense com alto grau de instrução e nível socioeconômico elevado, a UIC mediana foi de 221 μg/L classificando-as como estado nutricional suficiente de iodo (KATZ, et al, 2013).

Uma coorte de gestantes do Sri Lanka mostrou que o nível de iodo das mulheres foi adequado no início da gravidez, pois havia apenas 4,3% de mulheres grávidas com deficiência moderada de iodo (iodo urinário <50,0 μg/L). No entanto, com a progressão da gestação, houve declínio constante no status de iodo na urina materna e aumento no status de deficiência, e a diferença observada foi significativa (p <0,001). Esse declínio progressivo do nível de iodo na urina ocorreu com o avanço da idade gestacional. Essa redução na UIC pode estar atribuída à falta de homeostase entre o aumento da demanda e o suprimento de iodo com o avanço da gestação (DE ZOYSA; HETTIARACHCHI; LIYANAGE, 2016).

No Brasil, um número reduzido de investigações evidenciou a deficiência de iodo em gestantes. Corcino et al, (2019) mostraram que mulheres no primeiro e terceiro trimestre da gestação e que residiam em região brasileira considerada suficiente em iodo, apresentaram estado nutricional de iodo adequado com mediana de UIC de 221 μg/L e 208 μg/L respectivamente. Em estudo realizado no estado de São Paulo, 57% das 191 gestantes apresentaram deficiência de iodo (FERREIRA et al, 2014). Em outro estudo que avaliou a situação nutricional de iodo no grupo materno-infantil no município de Diamantina, região semiárida de Minas Gerais, foi estimada prevalência expressiva de deficiência entre gestantes e nutrizes, sendo 70% e 73%, respectivamente (MACEDO, 2017). Tais achados levantam dúvidas quanto à suficiência iódica nas gestantes brasileiras, o que merece atenção já que no ano de 2013, devido ao consumo excessivo de sal pela população brasileira e consequentemente, ingestão de iodo além dos níveis adequados pela população em geral, a Agência Nacional de Vigilância Sanitária (ANVISA) reduziu o teor da fortificação de iodo no sal de cozinha de 20 a 60 µg/kg para 15 a 45 µg/kg (BRASIL, 2013), o que pode ter dificultado ainda mais a ingestão adequada deste nutriente pela população de gestantes

3. Objetivos

3.1. Objetivo geral

Estimar a prevalência da ingestão insuficiente de iodo em gestantes de diferentes regiões do mundo por meio de revisão sistemática da literatura e meta-análise.

3.2. Objetivos específicos

- Investigar variações da medida sumário em subgrupos relevantes de acordo com características demográficas das gestantes e metodológicas dos estudos incluídos;
- Avaliar a qualidade dos estudos publicados sobre consumo insuficiente de iodo e gestantes.

4. Métodos

4.1. Tipo de estudo

A presente revisão sistemática com meta-análise foi conduzida conforme recomendações do PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) e seu protocolo foi registrado na plataforma PROSPERO (Prospective Register of Systematic Reviews) sob o código CRD42020153361.

4.2. Critérios de inclusão

Para a definição dos artigos elegíveis para a revisão, foram considerados os seguintes critérios:

a) Estudos realizados com gestantes adolescentes e adultas associados a ingestão de iodo em diferentes regiões do mundo;
b) Estudos que apresentam dados de prevalência da inadequação do estado nutricional de iodo na gestação, de acordo com os parâmetros recomendados pela OMS (2007);
c) Estudos observacionais realizados sobre deficiência de iodo em gestantes no mundo. Nos estudos de coorte, foram utilizados os dados de prevalência da linha de base que incluíram gestantes de todos os trimestres gestacionais.

4.3. Critérios de exclusão

Foram excluídos desta revisão:

a) Estudos que investigaram o estado nutricional de iodo em gestantes com histórico de doenças da tireoide e/ou outras doenças crônicas;
b) Estudos que apresentaram apenas dados de mediana de UIC;
c) Estudos com gestantes em uso de suplementos que contém iodo,
d) Estudos em animais, resumos de congresso, cartas aos editores, resenhas, opiniões pessoais, capítulos de livros, comentários, editoriais e qualquer publicação sem dados primários.
O apêndice 1 detalha as razões para exclusão dos estudos considerados não elegíveis.

4.4. Fontes de informação e estratégias de busca

A busca pelos artigos foi realizada nas seguintes fontes de dados: MEDLINE, Embase, Scopus, Web of Science, LILACS. A literatura cinzenta foi consultada por meio do Google Scholar e ProQuest Dissertations & Theses Global. Publicações até a data de 7 de novembro de 2019 foram analisadas e as buscas atualizadas na data de 23 de agosto de 2020.

A estratégia de busca foi revisada por um pesquisador com experiência em revisões sistemáticas, de acordo com o checklist PRESS (Peer Review of Electronic Search Strategies) (Apêndice 2).

A estratégia de busca utilizada e adaptada para bases de dados foi construída pelos seguintes descritores e operadores booleanos: pregnancy OR pregnancies OR gestation OR pregnant OR pregnant Women OR pregnant woman OR prenatal care OR pregnancy in adolescence OR teen pregnancy OR teen pregnancies OR adolescent pregnancy OR adolescent pregnancies AND iodine deficiency OR iodine insufficiency OR iodine status OR urinary iodine concentration OR serum iodine OR iodine OR iodine intake AND prevalence OR frequency OR percentage OR percent OR proportion OR ratio OR rate OR percentage AND survey OR cross-sectional studies OR cross-sectional OR observational OR cohort.

A busca realizada no Google Acadêmico se limitou aos primeiros 200 artigos mais relevantes. Nenhum dos filtros de idioma, data de publicação ou status foram aplicados aos resultados de cada base de dados. Mais informações acerca das estratégias de busca podem ser visualizadas no Apêndice 3.

4.5 Seleção dos estudos e extração dos dados

De acordo com os critérios de elegibilidade, duas pesquisadoras selecionaram os estudos, de forma independente, em duas etapas:

- ✓ Leitura dos títulos e resumos;
- ✓ Leitura do texto completo.

Após a seleção, as discordâncias foram resolvidas em reuniões de consenso. O quadro 3 elenca as informações que foram extraídas dos artigos selecionados e listadas em planilha eletrônica.

Quadro 3 – Informações extraídas dos estudos selecionados

Dados que foram extraídos	
✓Autores ✓ País e cidade ✓ Ano de coleta dos dados	✓ Tipo e tamanho da amostra ✓Trimestre gestacional ✓ Local de coleta de dados

✓ Data da publicação ✓ Desenho do estudo ✓ Existência de cálculo amostral	✓ Faixa etária ✓ Prevalência da ingestão insuficiente de iodo

Para remover os artigos em duplicata, foi utilizado o programa de gerenciamento de referências Mendeley e o aplicativo da web para revisões sistemáticas Rayyan (OUZZANI et al, 2016). Os dados foram extraídos independentemente por dois pesquisadores e registrados em planilha eletrônica Microsoft Excel 2016. Para minimizar a possibilidade de erros durante o processo de extração das informações, uma pesquisadora extraiu os dados e a outra fez a verificação.

4.6 Avaliação do risco de viés dos estudos

O intrumento *JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data* elaborado pelo Instituto Joanna Briggs foi utilizado para a avaliação do risco de viés dos estudos. Esse instrumento avalia nove itens em quatro perspectivas (sim, não, não está claro e não se aplica). Os itens são (em sua versão original, em inglês):

1. Was the sample frame appropriate to address the target population?

3. Was the sample size adequate?

4. Were the study subjects and the setting described in detail?

5. Was the data analysis conducted with sufficient coverage of the identified sample?

6. Were valid methods used for the identification of the condition?

7. Was the condition measured in a standard, reliable way for all participants?

8. Was there appropriate statistical analysis?

9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Para os estudos que apresentaram “Yes” como resposta para todos os itens avaliados, o risco de viés foi considerado baixo, e para aqueles que apresentaram “No” ou “Unclear” como resposta para algum item, foi considerado com alto risco de viés (apêndice 4). Não foram atribuídos escores e os dados foram apresentados por meio da análise da frequência relativa de cada domínio investigado. A avaliação do risco de viés não foi utilizada como critério de exclusão dos artigos, sendo parâmetro para estudo da heterogeneidade e da análise de subgrupos.

4.7 Análise dos dados

O desfecho primário foi a prevalência da ingestão insuficiente de iodo, com seu intervalo de confiança de 95% (IC 95%). Na fase qualitativa, foram identificados e relatados os principais resultados relacionados ao desfecho nos estudos primários, assim como suas principais características.

4.7.1 Metanálise e análise da heterogeneidade

A metanálise foi calculada utilizando-se um modelo de efeitos aleatórios e ponderada pelo inverso da variância. (RODRIGUES e ZIEGELMANN, 2010). Para a inspeção visual, foi construído o gráfico *forest plot* das prevalências e intervalos de confiança de cada estudo, assim como foi calculada a medida sumária para o conjunto dos mesmos.

A heterogeneidade foi avaliada pelo teste do qui-quadrado, sendo sua magnitude verificada pelo o i-quadrado (I^2). O teste do qui-quadrado é um dos mais empregados para avaliar a significância da heterogeneidade, sendo convencionado um nível de significância mais conservador de $p < 0,10$, em lugar do usual $p < 0,05$. Para valores de I^2 menores que 40%, a heterogeneidade não foi considerada importante (DEEKS et al, 2020).

4.7.2 Análise de subgrupos

A análise de subgrupos consiste em tentar explicar a heterogeneidade a partir de variáveis categóricas onde divide-se a amostra em dois ou mais grupos e avalia-se separadamente cada um desses subgrupos (DEEKS et al, 2020). Para tentar amenizar os efeitos da heterogeneidade foi estimado as medidas sumárias, com seus respectivos intervalos de confiança, para subgrupos definidos por:

- ✓ Região geográfica (África, América, Ásia, Eurásia, Europa e Oceania);
- ✓ Idade (adulto, adulto e adolescente, e não relatado);
- ✓ Trimestre gestacional (todos, primeiro, segundo, terceiro, primeiro e terceiro, e não relatado);
- ✓ Período de publicação (antes ou depois de 2010);
- ✓ Tamanho da amostra (<1000 ou >1000 gestantes);

- ✓ Risco de viés (alto ou baixo);
- ✓ Estado nutricional de iodo por país (suficiente ou insuficiente).

4.7.4. Meta-regressão

A meta-regressão é uma extensão para análises de subgrupos que permite verificar o efeito de variáveis contínuas, bem como categóricas, a serem investigadas e, em princípio, permite que os efeitos de múltiplos fatores sejam investigados simultaneamente (HIGGINS; THOMPSON, 2002). Com o objetivo de identificar as causas da heterogeneidade nos estudos incluídos, foi realizado meta-regressões utilizando o teste de Knapp e Hartung (2003), com significância de $p<0,05$, para testar as variáveis:

- ✓ Período de publicação (antes ou depois de 2010);
- ✓ Início da coleta de dados (ano);
- ✓ Tamanho da amostra (<1000 ou >1000);
- ✓ Risco de viés (alto ou baixo).

4.7.4 Análise do viés de publicação

Nas revisões sistemáticas a presença do viés de publicação pode ser identificada por meio de gráfico de funil e de testes estatísticos. Na representação do gráfico de funil, os resultados são plotados contra uma medida de precisão. Quando todos os estudos estimam um valor semelhante para o efeito, apresentam a dispersão dos resultados estreita à medida que a precisão aumenta, dando origem a uma forma semelhante a um funil (PEREIRA e GALVÃO, 2014; STERNE et al, 2011).

Entretanto, os estudos pouco precisos, em geral realizados com amostras de tamanho pequeno, poderão encontrar resultados positivos ou negativos (estatisticamente significativos ou não) por influência do acaso, o que pode comprometer os resultados. Caso estudos pequenos e grandes tenham seus resultados sempre publicados, eles terão distribuídos simetricamente. Geralmente os pequenos estudos ficam concentrados na parte mais larga e os de maior precisão, em geral em menor número, mais próximos do valor real e situados na parte mais estreita do funil. Mas há uma tendência de publicação somente daqueles que apresentam resultados considerados relevantes, o que também pode comprometer os resultados. Nesses casos usualmente encontra-se assimetria no funil (small-study effect) (PEREIRA e GALVÃO, 2014).

Foi avaliada a existência do efeito de estudos pequenos (small-study effect) por meio da inspeção visual do gráfico de funil e do cálculo do teste de Egger (STERNE et al, 2011), com significância de $p < 0,05$.

4.7.5 Softwares

As análises dos dados foram realizadas no pacote estatístico STATA® versão 15. (StataCorp LLC, College Station, TX, EUA), número de série: 301506206729.

5. Resultados

O resultado apresenta o artigo original submetido a revista European Journal of Clinical Nutrition ISSN 1476-5640 (online), fator de impacto: 3,29.

Review Article

Prevalence of insufficient iodine intake in pregnancy worldwide: A systematic review and meta-analysis

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Abstract

Context: Iodine deficiency in pregnant women is related to impaired foetal growth and development. **Objective:** To estimate the prevalence of insufficient iodine intake in pregnant women from different regions of the world. **Data Source:** Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, five electronic databases and Google Scholar grey literature were searched until August 2020. **Data Extraction:** Two reviewers independently conducted article selection, data extraction, and assessment of the risk of bias. **Data Analysis:** Meta-analyses with

random effects, subgroup analyses, and meta-regressions were performed. **Results:** In total, 4,443 articles were found, with 58 eligible for inclusion. The population consisted of 160,889 pregnant women adults and adolescents, and the overall prevalence of insufficient iodine intake was 53% (95% confidence interval [CI]: 46–59; I^2=99.8%). Pregnant women who live in insufficient iodine status country had a higher prevalence (82%; 95% CI: 70–94; I^2=97.7%) of inadequate iodine nutritional status than to those living in country considered sufficient (51%; 95% IC: 44–57; I^2=99.8%). **Conclusion:** Despite the progress in iodine fortification policies and periodic monitoring of the iodine nutritional status of the population worldwide, salt iodination alone may not be sufficient to provide adequate iodine status to pregnant women. Thus, other actions may be necessary to improve the nutritional clinical care of pregnant group.
Keywords: Iodine deficiency disorders; pregnant women; prevalence; systematic review

Introduction

Dietary iodine is an essential micronutrient for the synthesis of thyroid hormones and is especially important during pregnancy and early infant life because of its role in the development of the nervous system.[1] During pregnancy, the demand for iodine increases due to physiological changes, such as increased glomerular filtration, leading to increased urinary excretion, and before 20 weeks of gestation, the foetus cannot produce thyroid hormones independently.[2] Additionally, thyroid hormones play an essential role in neuronic migration, myelination, synaptic transmission, and brain plasticity in the foetus and neonate.[3]

The recommended iodine intake is 250 μg/day for pregnant women and 150 μg/day for non-pregnant women of reproductive age.[4] Insufficient iodine intake during pregnancy results in multiple metabolic and functional manifestations which interfere with human growth and development and are collectively termed as iodine deficiency disorders (IDDs).[4,5] The consequences of IDDs during pregnancy are increased risk of miscarriage and child mortality, foetal hypothyroidism, and serious adverse health-related effects, including cretinism and growth retardation. Nevertheless, adequate intake of iodine before the third trimester of pregnancy can reverse neurological impairment.[3,6]

Iodine deficiency remains a global public health problem and affects both developed and developing countries.[4] Despite the progress in eradicating iodine deficiency in many countries around the world through salt iodisation strategies, iodine deficiency remains a problem in pregnant women.[7] Women who live in iodine-sufficient countries usually start pregnancy with adequate intrathyroidal stocks and can handle the increased demands of iodine during pregnancy, if they maintain adequate dietary iodine intake. On the other hand, women who live in iodine-deficient countries may start their pregnancy with inadequate iodine reserves which are quickly depleted given the increased thyroid hormone synthesis, enhanced renal iodine clearance, and transplacental transfer of iodine to the fetus.[8,9]

A recent systematic review included studies published until 2017 and showed that the prevalence of insufficient iodine intake in pregnant women in the world ranged from 16.1% to 84.0%, and dietary iodine intake was lower than the WHO recommendations.[10] Although this review was well designed and conducted, the aim was to analyse only adult pregnant women, but it did not present a meta-analysis of the results. Since constant monitoring of the nutritional status of iodine during pregnancy helps to tackle and control iodine deficiency disorders in the mother-baby dyad, and there is no systematic review with meta-analysis of the results the worldwide prevalence of insufficient iodine intake during pregnancy, this study aimed to estimate the worldwide prevalence of insufficient iodine intake in adolescent and adult pregnant women to better support IDD prevention and control strategies for maternal and child groups.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA checklist[11] (Appendix S1).

Registration and Protocol

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42020153361.

Eligibility Criteria for the Studies

The eligibility criteria was cross-sectional and cohort studies that presented data the prevalence of insufficient iodine intake in pregnant women worldwide considering all gestational trimesters, where WHO (2007)[4] parameters were used, in which the urinary iodine concentration (UIC) <150 µg/L is classified as insufficient iodine intake. Participants under 19 years of age were considered adolescents (Table 1).

Table 1 - Participants, Exposure, Comparisons, Outcomes, and Study Design (PECOS) criteria

Parameter	**Criteria**
Participants	Pregnant women
Exposure	-
Comparisons	-
Outcomes	Insufficient iodine intake prevalence
Study design	Observational studies

Studies involving pregnant women with a history of thyroid and/or other chronic diseases or pregnant women taking iodine-containing supplements, studies with data presented only as median UIC, cohort studies that had pregnant women from only one gestational trimester at baseline, animal studies, letters to editors, congress abstracts, reviews, personal opinions, book chapters, comments, editorials, and publications without primary data were excluded. There was no restriction on the date of publication or the language used.

Information Sources

The search for information was performed on 22 October, 2019 and updated on 23 August, 2020. The electronic databases of Medline, Embase, Scopus, Web of Science, and Lilacs were used. The grey literature texts which met the eligibility criteria established in this review were examined using Google Scholar limited to the first 200 articles (listed in order of relevance) and ProQuest Dissertations & Theses Global. The reference lists of the selected articles were manually searched to identify studies not retrieved by the databases.

Search Strategy

The keywords used to construct the search strategy were identified in Medical Subject Headings and Health Sciences Descriptors. The search strategy was reviewed by researchers experienced in conducting systematic reviews according to the checklist of the Peer Review of Electronic Search Strategies (appendix 1).[12]

The following terms and Boolean operators were used in the search strategy: (pregnancy OR pregnancies OR gestation OR pregnant OR pregnant women OR pregnant woman OR prenatal care OR pregnancy in adolescence OR teen pregnancy OR teen pregnancies OR adolescent pregnancy OR adolescent pregnancies) AND (iodine deficiency OR iodine insufficiency OR iodine status OR urinary iodine concentration OR serum iodine OR iodine OR iodine intake) AND (prevalence OR frequency OR percentage OR percent OR proportion OR ratio OR rate OR percentage) AND (survey OR cross-sectional studies OR cross-sectional OR observational OR cohort). The search strategies according to the characteristics of each database are detailed in the appendix S2.

Studies Selection

According to the eligibility criteria, two reviewers (ESOP and ICCL) selected articles independently by reading titles and abstracts, after removing duplicate articles. Then, the two researchers read the full text of the previously selected articles. In cases of divergence between the researchers, the decision of including or excluding an article was made by consensus.

Extraction of Data

To minimise the possibility of errors during extraction, the data were extracted from the included articles by one researcher and verified by the other. The data were entered into an electronic spreadsheet containing the following fields: author's name, year of study, year of publication, country, study design, data collection location, age of the participants, sample size, trimester, timing of assessment, method of measurement of urinary iodine excretion, and prevalence of insufficient iodine intake. At least two attempts were made to request additional information from the authors when it was not available in the articles or when the full text was not available.

Assessment of the Risk of Bias

The JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data[13] by the Joanna Briggs Institute was used to assess the risk of bias. It consists of nine questions from four perspectives (yes, no, unclear and not applicable): (1) appropriate sample framework to address the target population, (2) appropriate sampling criteria, (3) adequate sample size, (4) study subjects and the setting described in detail, (5) analysis with sufficient coverage of the identified sample, (6) valid outcome measurement, (7) objective and standardized measurement criteria, (8) appropriate statistical analysis, and (9) strategies for properly dealing with the response rate.

For this study, when the response for all items was “yes”, the risk of bias was considered to be low, and if the response was “no” or “unclear” to any item, a high risk of bias was expected. No scores were assigned, and the data were presented through the analysis of the relative frequency of each investigated domain. The risk of bias assessment was not used as an exclusion criterion for the articles, although it was used as a parameter in the heterogeneity analysis.

Summary Measures and Synthesis of Results

The primary outcome of the analysis was the prevalence of insufficient iodine intake, with a 95% confidence interval (95% CI). Additionally, data regarding gestational trimesters, adult and adolescent subgroups, and geographic region were assessed for qualitative analysis.

The meta-analysis was calculated according to the random effects model by the DerSimonian–Laird method.[14] Heterogeneity was assessed using the chi-square test ($p < 0.10$), and its magnitude was verified by the Higgins and Thompson I-square (I^2).[15] When I^2 values were less than 40%, the heterogeneity was not considered important.[16] For visual inspection, forest plot graphs of prevalence and confidence intervals of each study were constructed, together with the estimation of the summary measurement.

Assessment of Heterogeneity and Publication Bias

Subgroup analyses and meta-regressions were performed to verify the source of heterogeneity in the studies included in the systematic review. In the subgroup analysis, the following covariables were used: period of publication (before or after 2010), geographic region (Africa, America, Asia, Eurasia, Europe, and Oceania), age (adult, adult and adolescent, and not reported), gestational trimester measured (all, first, second, third, first and third, and not reported), sample size (<1000 or >1000), risk of bias (high or low), and iodine status by country.

The period of publication covariable of the studies was categorized in before or after 2010 to assess the evolution of insufficient iodine intake in the last decade, and the sample size covariable was categorized in <1000 or >1000 to compare the effect of studies with small sample sizes or larger sample sizes on heterogeneity. Countries were categorized into iodine deficient or sufficient areas based on WHO global score data. [17] In the meta-regressions, the following covariables were used: period of publication (before or after 2010), start of data collection, sample size (<1000 or >1000), and risk of bias (high or low).

Publication bias was analysed using Egger regression with a 5% significance level and by funnel plot visual inspection.[18] Data analysis was performed using STATA® version 15.

Results

Selected Studies

A total of 4,443 records were retrieved from seven electronic databases, including the grey literature. After the duplicates were removed and the titles and abstracts were read, 231 potentially relevant studies were selected for full-text reading. A total of 173 studies were excluded for the reasons presented in Figure 1. The specific reasons for exclusion are detailed in Appendix S3. One article was added from the list of references of the selected records. Finally, 58 articles were considered in this review. A diagram of the screening process is shown in Figure 1.

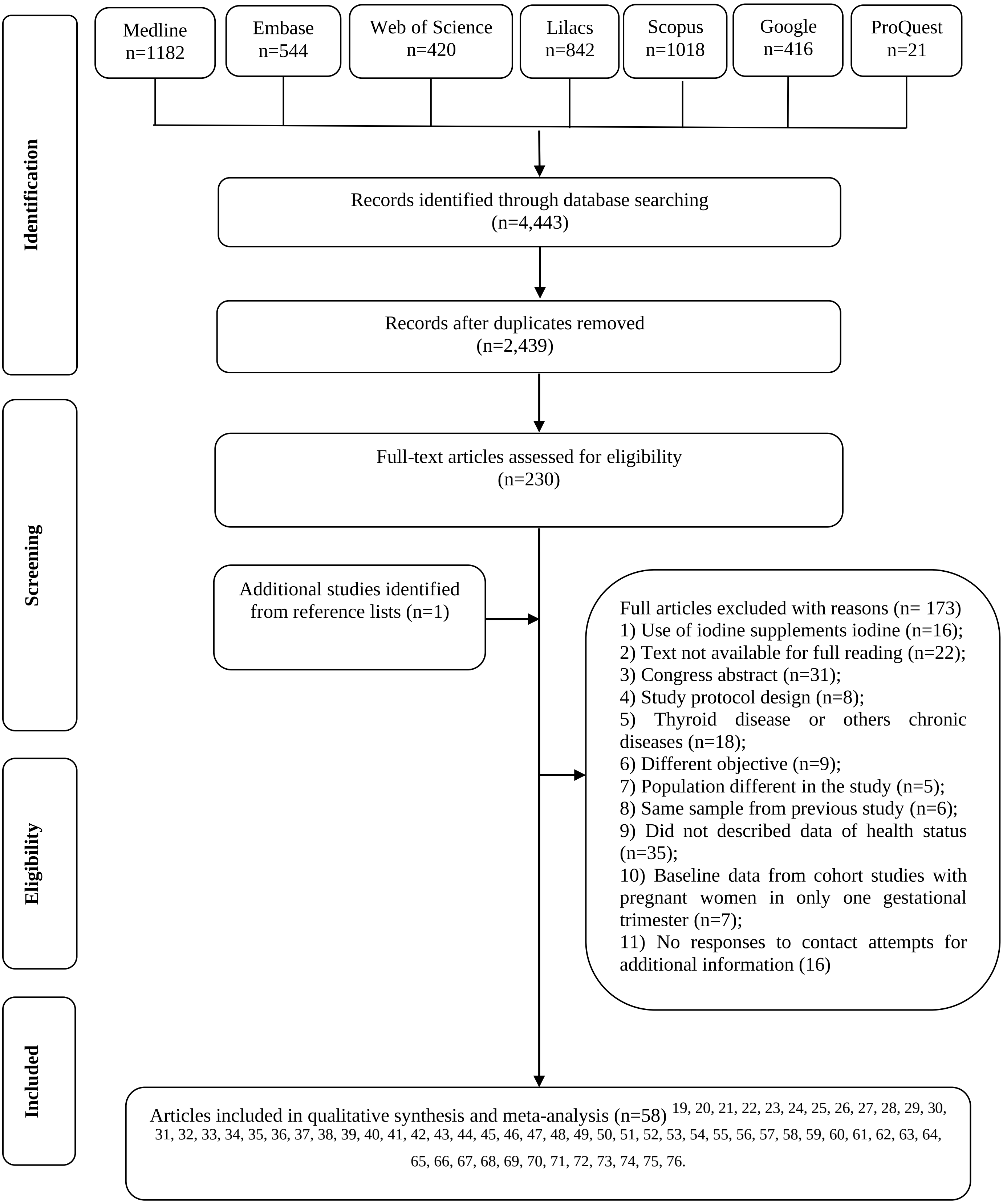

Figure 1 **- Flow chart of the literature search, selection criteria and inclusion of studies (Adapted from PRISMA).**

Characteristics of the Studies

Fifty-eight articles were published between 2008[19] and 2020.[20-26] Studies were conducted in the continents of Asia,[19,21-51] America,[52-57] Africa,[20,58-63] Europe,[64-69] Oceania,[70] and Eurasia.[71-76] Only four studies had a cohort design.[28,41,69,70] Regarding age, 33 studies[19-25,31-34,44,47-50,52,54-56,60,61,64-71,73-75] included adolescents in overall sample. The population included 160,889 pregnant women in all trimesters, aged from 15[19,23,34,49,54,65,67] to 50[34,75] years. Regarding gestational weeks, we considered a range from 7.0 (interquartile range [IQR], 5.9–8.6)[41] to 40 (IQR 34–42) weeks.[42] The minimum sample size was 24,[70] and the maximum sample size was 46,506 participants.[43] Table 2 summarises the main results of the studies.

Table 2 – Summary of characteristics of included studies

Author	Study Period/ Country	Geographic region	Study design	Location of data collection	Age (range or mean)	Gestational age (range or mean)	Sample size n=	Prevalence of insufficient iodine intake
Akdader-Oudahmanea et al, 2020[20]	2016-2017 Northern Algeria, North Africa	Africa	Cross-sectional	Hospital	22 - 44	27 ± 0.66	172	1 trimester: 23%; 2º trimester: 15%; 3º trimester: 24%
Azizi et al. 2011[27]	2005 - 2006 Teran, Iran	Asia	Cross-sectional	Community	25.1 ± 5.1	1st, 2nd and 3rd trimester (11.9 ± 3.6)	138	38%
Banza, et al. 2016[58]	2009 - 2011 Lumbumbashi, Congo	Africa	Cross-sectional	Hospital	NR	1st, 2nd and 3rd trimester	225	52%
Bílek, et al. 2016[64]	2010 - 2015 Czech Republic	Europe	Cross-sectional	Hospital	(18-44) 32 ± 5	1st, 2nd and 3rd trimester	532	52.3%
Bottaro et al. 2016[52]	2014 - 2015 Montevideu, Uruguay.	America	Cross-sectional	Hospital	> 18	1st, 2nd and 3rd trimester	94	38.5%
Caballero, 2011[53]	2007 - 2008 Trujillo, Venezuela	America	Cross-sectional	Primary health unit	NR	1st, 2nd and 3rd trimester	300	25%
Caldwell et al. 2013[54]	NHANES: 2005-2010 NCS: 2009-2010 - U.S	America	Cross-sectional	Community	15-44	1st, 2nd and 3rd trimester	NHANES (2007-2010): 76 NCS: 501	NHANES (2007-2010): 55.8% NCS: 45.3%
Celik et al. 2016[71]	2013 - 2014 Edirne, Turkey	Eurasia	Cross-sectional	Primary health unit	(17-41) 27.29 ± 5.17	First trimester (9.83 ±2.17)	275	88.4%
Çetinkaya et al. 2012[72]	2009 Erzurum, Turkey	Eurasia	Cross-sectional	University	(19-33) 26.5 ± 2.8	1st, 2nd and 3rd trimester	113	72.6%
Charoenratana et al. 2015[28]	2013 - 2014 Thailand	Asia	Prospective cohort	University	Group with iodine insufficiency: 28.26 ± 5.50. Group with iodine sufficiency: 28.13 ± 4.86.	1st, 2nd and 3rd trimester Insufficiency group: (28.26 ± 5.50) Sufficiency group: (28.13 ± 4.86)	399	43.6%
Delshad et al. 2016[29]	2013 - 2014 Iran	Asia	Cross-sectional	Antenatal clinic	(20-40) 27.1 ± 7.2	1st, 2nd and 3rd trimester (20.7 ± 10.0)	1072	78.2%
Gao et al, 2020[21]	2018-2019 - Zibo Gaoqing, Shandong, China	Asia	Cross-sectional	Hospital	30.3 ± 5.5	20.6 ± 8.5	534	58%
Gargari et al, 2020[22]	2015-2016 Theran, Iran	Asia	Cross-sectional	Hospital	20-45 years (29.14 ± 2.5)	38.4 ± 7.3	884	5,2%
Gowachirapant et al. 2009[30]	2007 - 2008 Bangkok, Thailand	Asia	Cross-sectional	Hospital	31.7 ± 4.8	1st, 2nd and 3rd trimester	302	69.2%

Table 2 - (continued)

Author	Study Period/ Country	Geographic region	Study design	Location of data collection	Age (range or mean)	Gestational age (range or mean)	Sample size n=	Prevalence of insufficient iodine intake
Grewal, Khadgawat & Gupta, 2013[31]	NR New Delhi, India	Asia	Cross-sectional	Hospital	(18-38) 26.35 ± 4.04	1st (11.4 ± 2.8) 2nd (26 ± 2.1) and 3rd (36.1 ± 2.0) trimester	150	2%
Hess et al. 2017[59]	2014 - 2015 Niger	Africa	Cross-sectional	Primary health unit	NR 27.7 ± 6.2	1st, 2nd and 3rd trimester	662	84.9%
Iqbal et al, 2019[47]	Not reported - Pakistan	Asia	Cross-sectional	Hospital	26 ± 4	not reported	80	68.8%
Jauhari et al, 2020[23]	2016-2017 Lucknow, India	Asia	Cross-sectional	Antenatal clinic	15-45 (24.5 ± 3.26)	1st, 2nd and 3rd trimester	200	19.0%
Ji et al, 2019[48]	2016-2018 - Harbin, Heilongjiang Province, China	Asia	Cross-sectional	Hospital	20 - 40 years	1st, 2nd and 3rd trimester	869	54.20%
Joshi et al. 2014[32]	2009 - 2010 Vadodara and Gujarat, India	Asia	Cross-sectional	Hospital	18 – 37 NR	First trimester	256	16.7%
Karakochuk et al. 2016[33]	2012 Prey Veng, Cambodia	Asia	Cross-sectional	Community	(18-45) 28.5 ± 4.6	NR	30	37%
Kasap et al. 2016[73]	2014 - 2015 Turkey	Eurasia	Cross-sectional	Hospital	(18-48) 26.3	1st, 2nd and 3rd trimester (18.4 ± 3.3)	135	28.1%
Kedir; Berhane & Worku, 2014[60]	2012 Haramaya District, Eastern Ethiopia	Africa	Cross-sectional	Community	(18-49) 27.0 ± 5.9	1st, 2nd and 3rd trimester (25.8 ± 5.8)	435	82.8%
Khan, 2019[69]	2008-2011 - Oslo, Norway	Europe	Retrospective cohort	Primary health unit	29.8 ± 4.9	1st, 2nd and 3rd trimester	681	78.8%
Khattak et al. 2018[34]	2012 Pakistan	Asia	Cross-sectional	Primary health unit	(15 - 50) 27.1	1st, 2nd and 3rd trimester	1246	58.7%
Kutlu and Kara, 2012[74]	2008 Turkey	Eurasia	Cross-sectional	Hospital	(16 – 41) 25 ± 4.6	Second trimester (12th and 18th week)	162	72.8%
Mabasa et al, 2019[63]	2012-2013 Mopani district, Limpopo province, South Africa	Africa	Cross-sectional	Primary health unit	Not reported	1st, 2nd and 3rd trimester	521	44.9%
Macedo, 2017[57]	2015 Brazil	America	Cross-sectional	Primary health unit	(22-32) 26,0 ± 6	3rd trimester (32,4 ± 5,9)	202	74,4%
Mackerras, Singh & Eastman, 2011[70]	Recruited: 1987-1990. Follow-up: 2005-2008 Darwin Region, Australia	Oceania	Prospective cohort	Hospital	(16–20) 17.8	NR	24	50%
Majumder, Arvinda & Chatterjee, 2014[35]	NR Kolkata, India	Asia	Cross-sectional	Hospital	(20-45) NR	1st, 2nd and 3rd trimester	237	37%
Majumder et al, 2019[49]	2017-2018, Tripura India	Asia	Cross-sectional	Community	15-47	3rd trimester	538	48.8%
Mao et al. 2015[36]	2011 Zhejiang province, China	Asia	Cross-sectional	Community	NR	1st, 2nd and 3rd trimester	430	61.6%
Mao et al. 2018[37]	2014 - 2015 Zhejiang, China	Asia	Cross-sectional	Community	(19-35) 28.0 ± 4.5	1st, 2nd and 3rd trimester	1304	59.3%

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Table 2 - (continued)

Author	Study Period/ Country	Geographic region	Study design	Location of data collection	Age (range or mean)	Gestational age (range or mean)	Sample size n=	Prevalence of insufficient iodine intake
Mioto et al. 2018[55]	2012 - 2016 Sao Paulo, Brazil	America	Cross-sectional	Hospital	(>18) 28.1 ± 6.5	1st, 2nd and 3rd trimester	273	52%
Oral et al. 2015[75]	2014 Istanbul, Turkey	Eurasia	Cross-sectional	Obstetrics centers	(18-50) 29.3 ± 5.6	1st, 2nd and 3rd trimester (25.4 ± 10.6)	3487	90.7%
Ozberk et al, 2018[76]	2014 - Konya, Turkey	Eurasia	Cross-sectional	Hospital	26.71 ± 5.27	1st, 2nd and 3rd trimester	107	57.9%
Pan et al 2019[49]	2016-2017 Tanjin, China	Asia	Cross-sectional	Obstetrics centers	18-44 - mean 28 (IQR 26-31)	1st, 2nd and 3rd trimester	1099	47.0%
Pelala et al, 2020[24]	2017-2018 Karnataka, India	Asia	Cross-sectional	Hospital	28 ± 7	3rd trimester	250	1.2%
Rao et al. 2018[38]	NR West Delhi, India	Asia	Cross-sectional	Community	NR 24.7 ± 4.5	3rd trimester (gestational age >28 weeks)	180	51.1%
Raverot, et al. 2011[65]	2008 - 2009 Lyon, France	Europe	Cross-sectional	Hospital	(15.3–45.7) 29.6 ± 5.6	1st, 2nd and 3rd trimester (21.8 ± 8.5)	100	77%
Rostami, Beiranvend & Nourooz-Zadeh 2012[39]	2009 Urmia County, Iran	Asia	Cross-sectional	Private clinic	NR 25.0 ± 5.0	1st, 2nd and 3rd trimester	811	Plains regions (1st and 3rd trimester): 84,5%; 66.9% Mountain regions (1st and 3rd trimester): 98.6%; 90.2%
Rostami et al, 2020[25]	Ziweh, Urmia, West Azerbaijan, Iran.	Asia	Cross-sectional	Primary health unit	17-40 (26.4±5.0)	1trimester	95	97.9%
Saraiva et al. 2018[56]	2014 - 2017 Rio de Janeiro, Brazil	America	Cross-sectional	Primary health unit	(18-35) 26.5 ± 5.0	1st trimester (9.0 ± 2.1)	244	48.2%
Sekitani et al. 2013[66]	NR Ukraine	Europe	Cross-sectional	Private clinic	(17 – 40) 25.9 ± 5.5	1st trimester (Mean 12.2)	148	96%
Simpong et al. 2016[61]	2013 - 2014 Ghana	Africa	Cross-sectional	Primary health unit	(18-45) 27.20 ± 5.99	1st, 2nd and 3rd trimester	120	42.5%
Singh, Foterdar & Lakshminarayana, 2008[19]	NR Rajasthan, India	Asia	Cross-sectional	Community	>15 years NR	Third trimester (>28 weeks)	384	58.8%
Stinca et al. 2017[62]	2014 - 2016 Marrakesh, Morocco	Africa	Cross-sectional	Primary health unit	(22–34) 27.0	(15–29) (Mean 21)	245	97%
Sultanalieva et al. 2010[40]	2007 Kyrgyzstan	Asia	Cross-sectional	Antenatal clinic	NR	1st, 2nd and 3rd trimester (Mean 22)	580	61 %

Table 2 - (continued)

Author	Study Period/ Country	Geographic region	Study design	Location of data collection	Age (range or mean)	Gestational age (range or mean)	Sample size n=	Prevalence of insufficient iodine intake
Sun et al. 2019[26]	2012-2014 Liaoning China	Asia	Cross-sectional	Community	19-40 NR	First trimester (4-8 weeks)	7073	48,2%
Tahirović et al. 2009[67]	2007 Tuzla, Bosnia	Europe	Cross-sectional	Private clinic	(15.4 - 45) 26.2	1st, 2nd and 3rd trimester	300	55%
Tam et al. 2017[41]	2014 - 2015 Hong Kong, China	Asia	Prospective cohort	Hospital	NR 31.3 ± 3.9	1st trimester Mean 7.0 (IQR 5.9-8.6)	437	71.5%
Torres et al. 2017[68]	2008 - 2009 Catalonia, Spain	Europe	Cross-sectional	Primary health unit	(>17) 31.0 ± 4.5	1st trimester	503	53.5%
Valizadeh et al. 2017[42]	2013 - 2014 Zanjan, Iran	Asia	Cross-sectional	Hospital	NR 26.3 ± 4.6	3rd trimester: 40 (IQR 34–42) weeks	394	73.1%
Yang et al, 2014[46]	2012 Henan, China	Asia	Cross-sectional	Hospital	≥ 19 (26.5 ± 5.7)	1st, 2nd and 3rd trimester	39.684	34.2%
Yang, et al. 2016[43]	2013 - 2014 Henan, China	Asia	Cross-sectional	Primary health unit	NR 2013: 26.6 ± 4.4 2014: 26.7 ± 4.2	1st, 2nd and 3rd trimester	2013: 40.223 2014: 46.506	2013: 30.1% 2014: 28%
Yanling et al. 2015[44]	2009 - 2010 Wuwei City, Gansu Province	Asia	Cross-sectional	Community	(18-45) NR	NR	85	Urban area: 25.5% Rural area: 44.1%
Yao et al, 2019[51]	2017 - Chongqing, China	Asia	Cross-sectional	Antenatal clinic	28 (± 5.26)	1st, 2nd and 3rd trimester	2580	40·97 %
Zhang et al. 2015[45]	2012 – China	Asia	Cross-sectional	Hospital	NR	1st, 2nd and 3rd trimester	1200	51.6%

NR: not reported

Risk of Bias within Individual Studies

The studies evaluated were considered heterogeneous in relation to risk of bias, and only 12 studies[22,23,29,34,43,46,54,57,59,60,73,75] (20%) were considered to have a low risk of bias. The parameters which frequently received the response of "Yes" were "Outcomes measured in a valid way" at 100% and "Analysis conducted with sufficient coverage of the identified sample" at 98.2%. Three parameters were not met by most studies: criteria for sampling in an appropriate way, study subjects and the setting described in detail, and adequate sample size (Figure 2 and appendix S4).

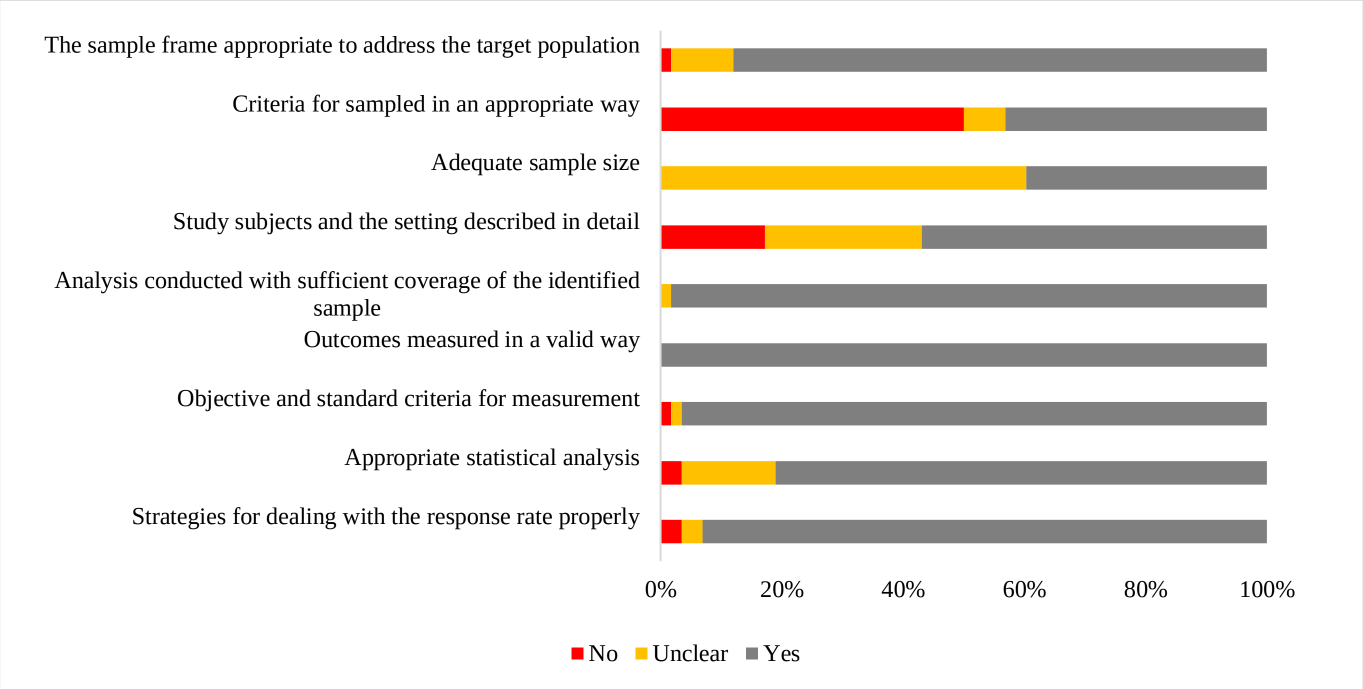

Figure 2 - **Risk of bias in the included studies.**

Results of Individual Studies

The prevalence of insufficient iodine intake in all three gestational trimesters was reported in 14 studies.[20,27,29,31,34,35,58,60-62,64,67,72,75] Among studies which included only pregnant women in the first trimester of pregnancy, the highest prevalence of insufficient iodine intake observed was 97.9%.[25] The prevalence of insufficient iodine intake ranged from 1.2% in India[24] to 98% in Iran.[39] Morocco,[62] Ukraine,[66] and Turkey[75] also showed high levels of insufficiency. Meanwhile, two studies conducted in India showed the lowest prevalence of insufficient iodine intake.[24,31] Among studies which included adolescents in the overall sample, there was no separation of data from adult and adolescent pregnant women, and the prevalence of insufficient iodine intake ranged from 2%[31] to 97.9%[25] (Table 2).

Regarding the measurement of urinary iodine excretion, the main methods used in the studies were as follows: Sandell–Kolthoff method,[20,22-27,29-34,38-40,42,45,48,52-55,57-60,62-67,70-76] arsenic-cerium catalytic spectrophotometer,[36,37, 43-46,50,51] inductively coupled mass spectrometry,[21,28,41,56] ammonium persulfate digestion method,[35,47,49,61,68] standard laboratory technique,[19] and colorimetric method.[69]

Meta-analysis of Results

To estimate the prevalence of insufficient iodine intake in pregnant women, 58 articles were included in the meta-analysis. The summary prevalence of insufficient iodine intake globally was 53% (95% CI: 46–59; I^2 = 99.8%) (Figure 3). In the subgroup analysis, considering the geographic region, the estimated prevalence was higher in Europe (72%; 95% IC: 57–87; I^2 = 98.7%) and Eurasia (69%; 95% IC: 55–84, I^2 = 98.4%) than in Asia (45%; 95% IC: 39–52; I^2 = 99.8%). The iodine status by country subgroup, the estimated prevalence was higher in countries with insufficient iodine status (82%; 95% IC: 70–94; I^2= 97.7%) than in countries with sufficient iodine status (51%; 95% IC: 44–57; I^2 = 99.8%). Among the other analysed subgroups, no statistical difference was observed (Table 3).

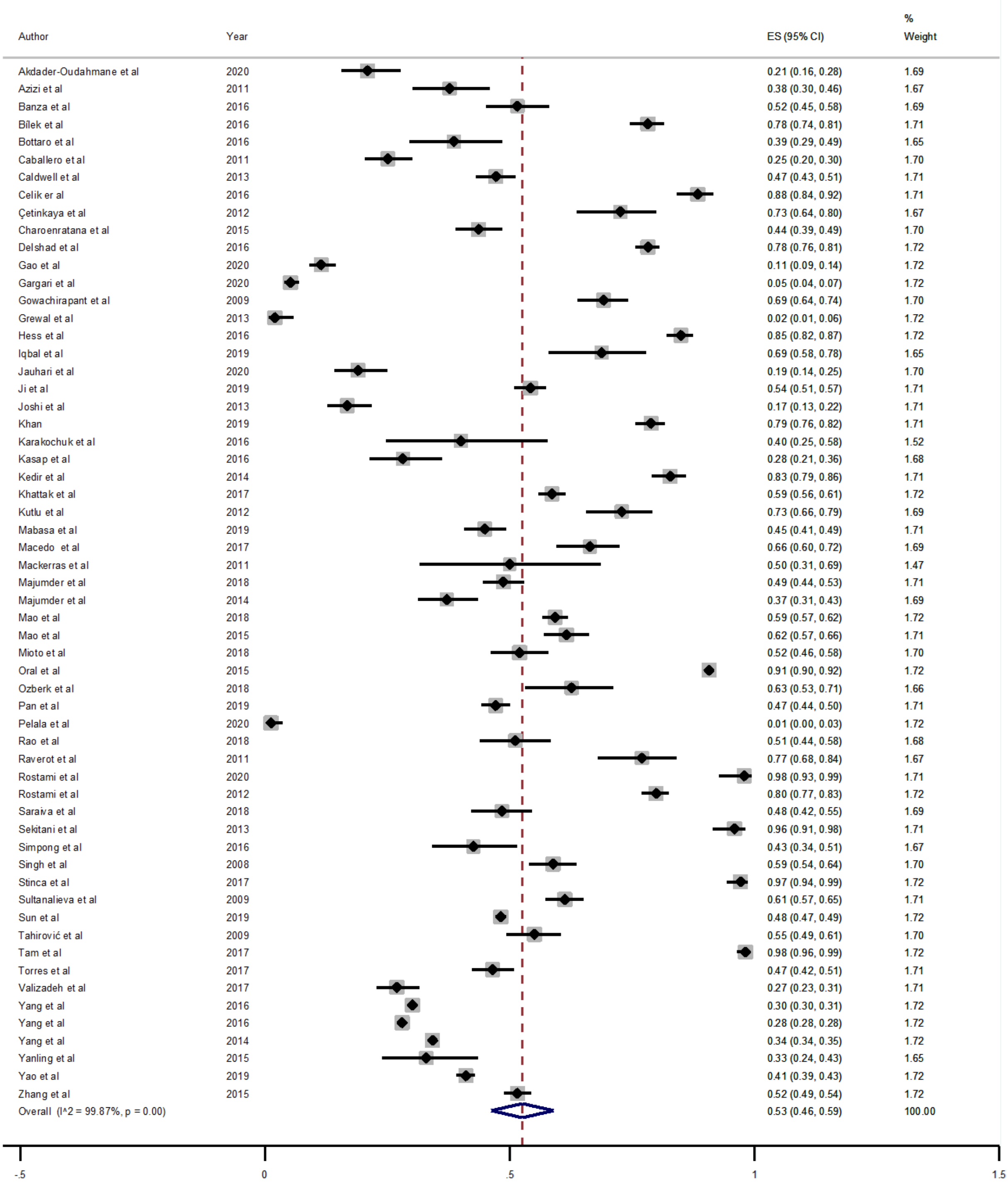

Figure 3 - **Prevalence of insufficient iodine intake in pregnancy in worldwide.**

Table 3 - **Prevalence of insufficient iodine intake and heterogeneity in subgroup analysis**

Subgroups	Number of studies	Number of participants	Prevalence (%)	95% CI	I^2 (%)	*p* (Chi-squared)
Period of publication						
Before 2010	17	5.541	55	45-65	99.90	0.00
After 2010	42	155.348	52	44-59	98.51	
Geographic region						
Asia	33	150.250	45	39-52	99.86	
Africa	7	2.380	61	42-80	99.42	
Europe	6	2.264	72	57-87	98.70	0.00
America	6	1.692	46	35-58	95.63	
Eurasia	6	4.279	69	55-84	98.48	
Oceania	1	24	50	31-69	Not observed	
Age						
Adult	16	141.655	60	51-70	99.92	
Adult and adolescent	33	14.964	50	36-64	99.85	0.00
Not reported	10	4.270	48	39-57	97.26	
Gestational trimester						
All	37	147.492	53	45-60	99.88	
First	7	8.594	63	41-85	99.72	
Third	7	2.832	37	21-53	99.56	0.00
First and Third	1	811	80	77-83	Not observed	
Not reported	4	219	48	29-68	88.22	
Sample size						
≤1000	48	15.415	53	41-64	99.80	0.00
>1000	11	145.474	52	41-62	99.94	
Risk of bias						
High	45	24.895	53	43-63	99.77	0.00
Low	14	135.994	52	42-63	99.94	
Iodine status by country						
Adequate or excessive	55	159.785	51	44-57	99.86	0.00
Insufficient	4	1.104	82	70-94	97.76	

In the meta-regression, none of the variables analysed could explain the high heterogeneity found in the analysis of the studies ($p > 0.05$). The funnel plot (Figure 4) showed asymmetry among the studies, which was confirmed by the Egger test ($p = 0.010$).

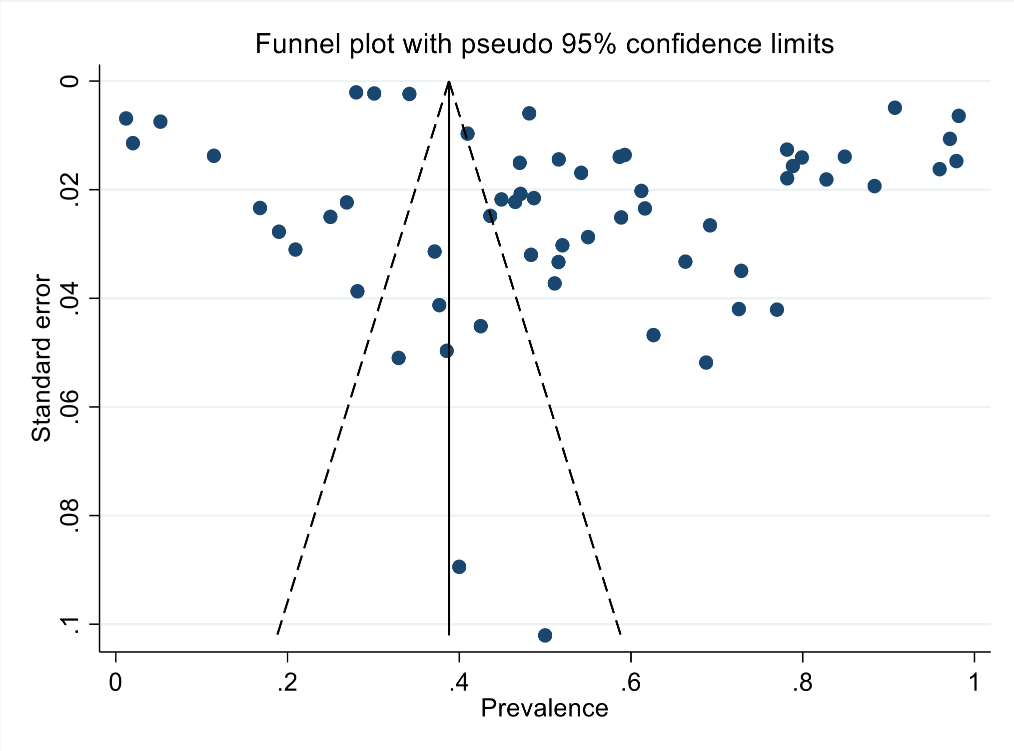

Figure 4 - **Funnel graph on the publication bias.**

Discussion

The main findings of this systematic review provide an overall estimate of the prevalence of insufficient iodine intake during pregnancy according to current WHO parameters. The meta-analysis results of the included studies indicate that the prevalence of insufficient iodine intake among pregnant women is 53%. Furthermore, this high prevalence of iodine insufficiency occurred in all six continents evaluated and the prevalence of inadequate iodine status was higher in insufficient country then adequate iodine country according to the WHO global score,[17] which reinforces the importance of health systems for monitoring public policies to eradicate iodine deficiency.

Since 1993, the WHO and United Nations Children's Fund have recommended universal iodisation of salt as a safe, sustainable, inexpensive, and easily implemented strategy to eliminate IDDs in almost all countries.[77] According to Gorstein et al.[78], worldwide, there was an overall reduction of 75.9% in cases of clinical IDDs associated with the implementation of universal salt iodination programs between 1993 and 2019. With this improvement in iodine status, a potential annual global economic benefit of almost $33 billion is estimated, with the costs of medical treatment of these disorders as well as the improvement in cognitive development during childhood taken into consideration.

Even with this progress, our findings show a high prevalence of insufficient iodine intake among pregnant women. In the subgroup analysis, the prevalence of insufficient iodine intake was higher in studies carried out in Europe and Eurasia than in those conducted in Asia. A study by Zimmermann et al,[79] to assess the prevalence of iodine deficiency during pregnancy at the national level in the countries of the Europe, estimated that pregnant women from two-thirds of the countries with available data had inadequate iodine intake corroborated by the high prevalence in our data. The lack of continuous monitoring of salt iodization programs contributes to reduction of their effectiveness and makes it impossible to determine whether they are sufficient to improve the iodine status of pregnant women. In addition, although pregnant women in some regions of Europe receive iodine-containing supplements, as most women discover they are pregnant at the end of the first trimester, supplementation generally does not cover the first trimester, when the developing foetal brain is especially vulnerable.[79] In light of this evidence, there is a need for adjustments in program monitoring to ensure that at least 90% of the population uses iodised salt properly, as recommended by the WHO[4], and iodine supplementation can be considered for pregnant women in order to complement the needs of these women in that specific period of life.[80]

At the global level, the American continent is the only one to have achieved significant progress in iodine deficiency control; however, there have been setbacks in some developing countries owing to the lack of sustainability of the programs.[81] The continuous implementation of information, education, communication, and social mobilisation strategies; updating the legal parameters related to iodine levels of salt intended for human consumption; and regular monitoring of iodine content in salt for human consumption are effective strategies which can assist in the global prevention of IDDs.[4]

An estimated 4.8 million newborns had IDDs in 2019, and this will cause irreversible loss throughout their lives.[78] Iodine deficiency during pregnancy is an important problem and, in some cases, has irreversible outcomes for the mother-baby dyad, such as increased risk of miscarriage, stillbirth, neonatal mortality, and delayed intrauterine growth.[3] The most severe form of disability results in endemic cretinism with permanently compromised physical and cognitive development.[5] A cohort study conducted in China with 2,087 adult pregnant women found that maternal iodine insufficiency occurred in early pregnancy and negatively affected foetal growth.[82] Of note, China is considered to have adequate iodine sufficiency status, yet the evaluated pregnant women reported insufficient iodine intake.

Despite the advances in health policies in reducing iodine deficiency, almost 30% of the households in the world consume insufficient amounts of iodised salt and fortified foods.[4] The data of the US National Health and Nutrition Examination Survey (NHANES) 2005–2010[53], showed a prevalence of 55% of insufficient iodine intake among pregnant women in the USA, which is considered an iodine-sufficient country , and the median UIC of pregnant participants was 129 μg/L, suggesting inadequate iodine intake.[53] A systematic review in 2019 observed insufficient iodine intake in 75% of the studies from different regions of the world but did not classify the severity of iodine deficiency in pregnant women.[10] Taken together, these results suggest that iodine deficiency is not restricted to the poorest regions and also affects developed countries, usually considered as regions with adequate iodine status. Our data showed that over half of the pregnant women in such regions presented with insufficient iodine intake.

Currently, salt iodination is the most widely used fortification strategy to treat IDDs worldwide for all population groups. Due to the increased demand for iodine for the production of thyroid hormones and the reduction of salt intake, pregnant women are considered a susceptible group.[83,84] In a study conducted by Yaman et al.[85] in Turkey, an adequate iodine status country, new-borns, and the mothers were assessed using the relationship between urinary status of maternal and foetal iodine and neonatal TSH levels, and it was found that despite 99% of the mothers using iodised salt during pregnancy, 56.8% were iodine deficient. This finding shows that although the universal salt iodisation program is effective for the majority of the population groups, this strategy alone may not be sufficient to ensure adequate iodine intake in the pregnant population. Therefore, the WHO recommendation of monitoring the population's iodine status through surveys of school-age children[4], may not reflect the real iodine nutritional status of pregnant women.[86]

The use of oral iodine supplements may be a good strategy to increase iodine intake during pregnancy.[80,87] However, there is no consensus regarding the need for oral iodine supplements in pregnant women due to the lack of robust evidence. While the American Thyroid Association recommends iodine supplementation during pregnancy,[87] the WHO understands that countries with established iodised salt programs do not need to recommend iodine supplements to the pregnant group.[4] Nowadays, with the salt-iodization programs, severe iodine deficiency is rare, but mild-to-moderate deficiency is still prevalent, as suggested by observational studies,[88] corroborated by the high prevalence in our data.

A systematic review by Dineva et al.[89] examined the effects of iodine supplementation in pregnant women with mild-to-moderate iodine deficiency (defined as

UIC range 50–149 μg/L) on maternal and infant thyroid disorders and child cognition. They found no significant benefits of iodine supplementation and concluded that there is insufficient good-quality evidence to support iodine supplementation in pregnancy in areas of mild-to-moderate deficiency. However, there are some limitations considering that in most studies, women began supplementation around the end of the first trimester, when the brain and neurological development is almost complete, and the randomised controlled trials included in the review were largely heterogenous. Thus, the ideal time to start supplementation, the iodine dose, and the baseline UIC values at the beginning of pregnancy should be considered to support iodine supplementation in pregnant women.

This is the first systematic review with a meta-analysis of the results of studies on iodine deficiency among pregnant women conducted in all continents, using a large number of observational studies. The strength of this review includes the use of methodologies based on current recommendations for the preparation of a systematic review with a meta-analysis of the results. We searched academic literature, including the grey literature, without restrictions on language and date of publication, and carried out the selection and extraction of data independently. Only studies which used the same references to classify the measurement of nutritional status of iodine were included. In addition, to ensure representativeness of the sample, the analyses included studies which evaluated pregnant women from public and private institutions from different continents, and the assessment of the risk of bias in all eligible studies was performed using an appropriate instrument.

Regarding the possible limitations of this review, some studies did not present all the data necessary for the analyses of subgroups and meta-regression, and the authors did not respond to contact attempts. In this review, the analysis of the current prevalence of insufficient iodine intake is complex because of publication bias and large heterogeneity between studies. To mitigate this result, subgroup analysis and meta-regression were performed; however, the subgroups were still heterogeneous and meta-regression was unable to identify the sources of this heterogeneity. However, the results showed publication bias, and the Egger test suggested that the small studies were the source of bias. Meta-analysis conducted with observational studies generally yields similar results,[90,91] indicating the limitations in the applicability of their results, without invalidating them. In the case of our study, the results can be used as an important monitoring and alerting tool by public health authorities to expand the scope of actions for elimination of IDDs in the pregnant population and improve clinical nutrition practises.

Conclusion

The overall prevalence of insufficient iodine intake in pregnant women was estimated to be 53%. Despite the progress in iodine fortification policies and periodic monitoring of the iodine nutritional status of the population in different countries, salt iodination by itself may not be sufficient to ensure adequate iodine intake among pregnant women. Thus, other steps including iodine supplementation must be taken to improve the nutritional care of pregnant women and reduce the risk of iodine deficiency disorders to the foetus.

Author contributions. 1) E.S.O. Patriota, I.C.C. Lima, V.S.S. Gonçalves and N. Pizato contributed significantly to the work's conception, design, data collection (as applicable), or data interpretation and analysis; 2) E.A.F. Nilson and S.C.C. Franceschini participated in the writing or critical revision of the article in a manner sufficient to establish ownership of the intellectual content; and 3) E.S.O. Patriota, I.C.C. Lima, E.A.F. Nilson, S.C.C. Franceschini, V.S.S. Gonçalves and N. Pizato read and approved the version of the manuscript being submitted.

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Compliance with ethical standards

Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

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Apendix S1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA checklist

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, figure 1, and Supplementary Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, and Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 and Supplementary Appendix 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page
TITLE			
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, Figure 2, and Supplementary Appendix 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8, and Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, and Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8, and Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6

From: Moher et al.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

Appendix S2. Database search strategy.

DATABASE	**SEARCH** (date)
MEDLINE	(("pregnancy"[MeSH] OR "pregnancy"[All Fields]) OR ("pregnancy"[MeSH] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields]) OR ("pregnancy"[MeSH] OR "pregnancy"[All Fields] OR "gestation"[All Fields]) OR ("gravidity"[MeSH] OR "gravidity"[All Fields] OR "pregnant"[All Fields]) OR "Pregnant Women"[All Fields] OR "pregnant woman"[All Fields] OR "Prenatal Care"[All Fields] OR "Pregnancy in Adolescence"[All Fields] OR "Teen Pregnancy"[All Fields] OR "Teen Pregnancies"[All Fields] OR "Adolescent Pregnancy"[All Fields] OR "Adolescent Pregnancies"[All Fields]) AND ("Iodine deficiency"[All Fields] OR "Iodine insufficiency"[All Fields] OR "Iodine status"[All Fields] OR "Urinary Iodine Concentration"[All Fields] OR "serum iodine"[All Fields] OR ("iodine"[MeSH] OR "iodine"[All Fields] OR "iodides"[MeSH] OR "iodides"[All Fields]) OR "iodine intake"[All Fields]) AND (("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "frequency"[All Fields] OR "epidemiology"[MeSH] OR "frequency"[All Fields]) OR Percentage[All Fields] OR Percent[All Fields] OR Proportion[All Fields] OR ("Ratio (Oxf)"[Journal] OR "ratio"[All Fields]) OR ("J Rehabil Assist Technol Eng"[Journal] OR "rate"[All Fields])) AND (("surveys and questionnaires"[MeSH] OR ("surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "survey"[All Fields]) OR "Cross-sectional studies"[All Fields] OR "Cross-sectional"[All Fields] OR Observational[All Fields] OR ("cohort studies"[MeSH] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields]))
EMBASE	(pregnancy OR pregnancies OR gestation OR pregnant OR 'pregnant women' OR 'pregnant woman' OR 'prenatal care' OR 'pregnancy in adolescence' OR 'teen pregnancy' OR 'teen pregnancies' OR 'adolescent pregnancy' OR 'adolescent pregnancies') AND ('iodine deficiency' OR 'iodine insufficiency' OR 'iodine status' OR 'urinary iodine concentration' OR 'serum iodine' OR iodine OR 'iodine intake') AND (prevalence OR frequency OR percentage OR percent OR proportion OR ratio OR rate) AND (survey OR 'cross-sectional studies' OR 'cross-sectional' OR observational OR cohort)
LILACS	(Pregnancy OR Pregnancies OR Gestation OR Pregnant OR “Pregnant Women” OR “pregnant woman” OR “Prenatal Care” OR “Pregnancy in Adolescence” OR “Teen Pregnancy” OR “Teen Pregnancies” OR “Adolescent Pregnancy” OR “Adolescent Pregnancies”) AND (“Iodine deficiency” OR “Iodine insufficiency” OR “Iodine status” OR “Urinary Iodine Concentration” OR “serum iodine” OR iodine OR "iodine intake") AND (Prevalence OR Frequency OR Percentage OR Percent OR Proportion OR Ratio OR Rate) AND (Survey OR “Cross-sectional studies” OR “Cross-sectional” OR Observational OR Cohort)
SCOPUS	TITLE-ABS-KEY (pregnancy OR pregnancies OR gestation OR pregnant OR "Pregnant Women" OR "pregnant woman" OR "Prenatal Care" OR "Pregnancy in Adolescence" OR "Teen Pregnancy" OR "Teen Pregnancies" OR "Adolescent Pregnancy" OR "Adolescent Pregnancies") AND "Iodine deficiency" OR "Iodine insufficiency" OR "Iodine status" OR "Urinary Iodine Concentration" OR "serum iodine" OR iodine OR "iodine intake" AND prevalence OR frequency OR percentage OR percent OR proportion OR ratio OR rate OR percentage AND survey OR "Cross-sectional studies" OR "Cross-sectional" OR observational OR cohort)

DATABASE	**SEARCH** (date)
WEB OF SCIENCE	TÓPICO: (Pregnancy OR Pregnancies OR Gestation OR Pregnant OR “Pregnant Women” OR “pregnant woman” OR “Prenatal Care” OR “Pregnancy in Adolescence” OR “Teen Pregnancy” OR “Teen Pregnancies” OR “Adolescent Pregnancy” OR “Adolescent Pregnancies”) AND TÓPICO: (“Iodine deficiency” OR “Iodine insufficiency” OR “Iodine status” OR “Urinary Iodine Concentration” OR “serum iodine” OR iodine OR "iodine intake") AND TÓPICO: (Prevalence OR Frequency OR Percentage OR Percent OR Proportion OR Ratio OR Rate OR Percentage) AND TÓPICO: (Survey OR “Cross-sectional studies” OR “Cross-sectional” OR Observational OR Cohort)
GOOGLE SCHOLAR	(Pregnancy OR “Pregnant Women” OR “Pregnant Adolescence”) AND (“Iodine status” OR “Urinary Iodine Concentration” OR “serum iodine” OR iodine) AND (Prevalence OR Frequency OR Ratio) AND (“Cross-sectional” OR Observational OR Cohort)
ProQuest	noft(Pregnancy OR Pregnancies OR Gestation OR Pregnant OR "Pregnant Women" OR "pregnant woman" OR "Prenatal Care" OR "Pregnancy in Adolescence" OR "Teen Pregnancy" OR "Teen Pregnancies" OR "Adolescent Pregnancy" OR "Adolescent Pregnancies") AND noft("Iodine deficiency" OR "Iodine insufficiency" OR "Iodine status" OR "Urinary Iodine Concentration" OR "serum iodine" OR iodine OR "iodine intake") AND noft(Prevalence OR Frequency OR Percentage OR Percent OR Proportion OR Ratio OR Rate) AND noft(Survey OR "Cross-sectional studies" OR "Cross-sectional" OR Observational OR Cohort)

Appendix S3 Excluded articles and reasons for exclusion.

Author, Year, Reference	Reason for exclusion
Andersson, 2010[1]; Andersson, 2019[2]; Dutta, 2016[3]; Fereja, 2018[4]; García-Solís, 2011[5]; Gunnarsdottir, 2013[6]; Huang, 2020[7]; Jaiswal, 2014[8]; Kapil, 2014[9]; Katko, 2018[10]; Kusic, 2012[11]; Nazeri, 2016[12]; Pettigrew-Porter, 2011[13]; Rafaat and Azzeh, 2020[14]; Wang, 2020[15]; Zhou, 2018[16]	1
Aikebaier, 2018[17]; Bodzek, 2006[18]; Bradbury, 2011[19]; Cao, 2009[20]; Cao, 2012[21]; Chen, 2011[22]; Chen, 2015[23]; Cheng, 2014[24]; He, 2014[25]; Hou, 2013[26]; Krzyczkowska-Sendrakowska, 1993[27]; Li, 2009[28]; Li, 2012[29]; Li, 2014[30]; Mao, 2013[31]; Mo, 2013[32]; Pruenglampoo, 1996[33]; Wang, 2008[34]; Wang, 2011[35]; Wang, 2014[36]; Yu, 2011[37]; Zheng, 2013[38]	2
Abel, 2020[39]; Alvarez-Pedrerol, 2009[40]; Bath, 2013[41]; Bouga, 2019[42] ; Brantsaeter, 2009[43]; Caldwell, 2016[44]; Castillo, 2018[45]; Eriksson, 2018[46]; Farebrother, 2017[47]; Fisher, 2013[48]; Garrett, 2013[49]; Gunnarsdottir, 2011[50]; Habimana, 2009[51]; Hutchings, 2017[52]; Huynh, 2015[53]; Konrade, 2014[54]; Kutlu, 2012[55]; Manousou, 2017[56]; McMullan, 2018[57]; Mullan, 2017[58]; Rayman, 2015[59]; Rosen, 2020[60]; Sav, 2016[61]; Serafico, 2013[62]; Souza, 2015[63]; Subhodip, 2017[64]; Tang, 2016[65]; Turgay, 2016[66]; Vidal, 2014[67]; Ward, 2015[68]; Zhabjaku, 2016[69]	3
Cuellar-Rufino, 2017[70]; Du, 2014[71]; Ivanova, 2013[72]; Liu, 2020[73]; Pearce, 2019[74]; Sadou, 2014[75]; Shamim, 2012[76]; Skeaff, 2011[77]	4
Derakhshan, 2018[78]; Dold, 2018[79]; Ferreira, 2014[80]; Lim, 2016[81]; Lindorfer, 2014[82]; Marco, 2010[83]; Nazarpour, 2020[84]; Olivares, 2012[85]; Ovadia, 2017[86]; Perlas, 2017[87]; Petry, 2019[88]; Rebagliato, 2010[89]; Sang, 2012[90]; Snart, 2020[91]; Takele, 2018[92]; Wang, 2018[93]; Yu, 2020[94]; Zhang, 2017[95]	5
Abel, 2017[96]; Bath, 2017[97]; Carrillo, 2015[98]; Carrillo, 2017[99]; Kianpour, 2019[100]; Kianpour, 2019[101]; Kippler, 2016[102]; Murillo-Liorente, 2020[103]; Perrine, 2019[104]	6
Hess, 2017[105]; Jayatissa, 2020[106]; Mills, 2019[107]; Tahirović, 2009[108]; Vijay, 2020[109]	7
Corcino, 2019[110]; Li, 2016[111]; Morais, 2020[112]; Rostami, 2012[113]; Snart, 2019[114]; Sultanalieva, 2010[115]	8
Aakre, 2015[116]; Abel, 2018[117]; Adalsteinsdottir, 2020[118]; Anaforoglu, 2016[119]; Ategbo, 2008[120]; Bath, 2013[121]; Bath, 2015[122]; Blumenthal, 2012[123]; Charlton, 2010[124]; Chen, 2018[125]; Dahl, 2018[126]; Dineva, 2019[127]; Egri, 2009[128]; Fereja, 2018[129]; Fuse, 2013[130]; Katz, 2013[131]; Kianpour, 2018[132]; Koyuncu, 2019[133]; Lou, 2020[134]; Manousou, 2019[135]; Mao, 2015[136]; Olivares, 2009[137]; Rahman, 2011[138]; ohner, 2020[139]; Shi, 2015[140]; Trofimiuk-Müldner, 2020[141]; Tuccilli, 2018[142]; Soares, 2008[143]; Vila, 2011[144]; Vongchana, 2018[145]; Wang, 2009[146]; Wang, 2017[147]; Wang, 2019[148]; Yang, 2018[149]; Zou, 2012[150]	9
Aguayo, 2013[151]; Castilla, 2018[152]; Lean, 2014[153]; Orito, 2009[154]; Simpong, 2018[155]; Xiao, 2018[156]; Zhang, 2019[157]	10

Author, Year, Reference	Reason for exclusion
Andersen, 2013[158]; Azzeh and Refaat, 2020[159]; Chen, 2015[160]; Granfors, 2015[161]; Henjum, 2018[162]; Hutchings, 2019[163]; Jaiswal, 2014[164]; Kirkegaard-Klitbo, 2016[165]; Knight, 2017[166]; Mateo, 2011[167]; Ozzola, 2016[168]; Rohner, 2016[169]; Stinca, 2017[170]; Sun, 2020[171]; Yan, 2011[172]; Yang, 2013[173]	11

Legend: (1) Use of supplements containing iodine; (2) Text not available for full reading; (3) Congress abstract; (4) Study design; (5) Thyroid disease or others chronic disease; (6) Different objective; (7) Population different in the study; (8) Same sample from previous study; (9) Did not described data of health status; (10) Baseline data with pregnant women only in the 1st trimester; (11) No responses to contact attempts for additional information.

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Appendix S4 Risk of bias for each individual study assessed by Joanna Briggs Institute critical appraisal checklist for prevalence studies.

Studies	Criteria								
	1*	2*	3*	4*	5*	6*	7*	8*	9*
Akdader-Oudahmane et al, 2020	Y	Y	U	N	Y	Y	Y	Y	Y
Azizi, 2011	Y	N	U	U	Y	Y	Y	Y	Y
Banza, 2016	Y	N	U	U	Y	Y	Y	U	Y
Bílek, 2016	Y	N	U	Y	Y	Y	Y	U	Y
Bottaro, 2016	Y	N	Y	Y	Y	Y	Y	U	Y
Caballero, 2011	U	Y	U	U	Y	Y	Y	U	Y
Caldwell, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y
Celik, 2016	Y	N	U	Y	Y	Y	Y	Y	Y
Çetinkaya, 2012	Y	U	U	Y	Y	Y	Y	Y	Y
Charoenratana, 2015	Y	N	U	Y	Y	Y	Y	Y	Y
Delshad, 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gao et al, 2020	Y	N	U	N	Y	Y	Y	Y	Y
Gargari et al, 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gowachirapant, 2009	Y	U	U	Y	Y	Y	Y	Y	Y
Grewal, 2013	Y	N	U	N	Y	Y	Y	U	Y
Hess, 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y
Iqbal et al, 2019	Y	N	Y	Y	Y	Y	Y	Y	Y
Jauhari et al, 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ji et al, 2019	Y	N	U	N	Y	Y	Y	Y	Y
Joshi, 2013	Y	N	U	Y	Y	Y	Y	U	Y
Khan et al, 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y
Karakouchu, 2016	U	Y	Y	Y	Y	Y	Y	Y	Y
Kasap, 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kedir, 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y
Khattak, 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kutlu, 2012	U	N	U	Y	Y	Y	Y	Y	Y
Mabasa et al	Y	N	U	Y	Y	Y	Y	Y	Y
Macedo, 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mackerras, 2011	Y	N	U	N	Y	Y	N	Y	N
Majumder, Arvinda & Chatterjee, 2014	Y	N	U	U	Y	Y	Y	U	Y
Majumder et al, 2019	Y	N	U	N	Y	Y	Y	N	Y
Mao, 2015	N	Y	U	U	Y	Y	Y	Y	Y
Mao, 2018	Y	Y	Y	U	Y	Y	Y	Y	Y
Mioto, 2018	Y	N	U	U	Y	Y	Y	Y	Y
Oral, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ozberk et al, 2018	Y	N	U	Y	Y	Y	Y	Y	Y
Pan et al, 2019	Y	N	U	N	Y	Y	Y	Y	Y
Pelala et al, 2020	Y	N	U	Y	Y	Y	Y	Y	Y
Rao, 2018	U	N	U	U	Y	Y	Y	N	Y
Raverote, 2011	Y	N	U	U	U	Y	U	Y	N
Rostami, 2012	Y	Y	Y	U	Y	Y	Y	Y	Y
Rostami et al, 2020	Y	Y	U	N	Y	Y	Y	Y	Y
Saraiva, 2018	Y	N	U	Y	Y	Y	Y	Y	Y
Sekitani, 2013	U	N	U	U	Y	Y	Y	Y	Y
Simpong, 2016	Y	N	U	Y	Y	Y	Y	Y	Y
Singh, 2008	Y	Y	Y	Y	Y	Y	Y	U	Y
Stinca, 2017	Y	N	Y	Y	Y	Y	Y	Y	Y
Sultanalieva, 2009	Y	N	Y	U	Y	Y	Y	Y	Y
Sun, 2019	Y	U	U	N	Y	Y	Y	Y	Y
Tahirović, 2009	Y	Y	U	Y	Y	Y	Y	Y	Y
Tam, 2017	Y	N	U	Y	Y	Y	Y	Y	Y
Torres, 2017	Y	N	Y	Y	Y	Y	Y	Y	Y
Valizadeh, 2017	Y	U	U	U	Y	Y	Y	Y	Y

Studies	Criteria								
	1*	**2***	**3***	**4***	**5***	**6***	**7***	**8***	**9***
Yang, 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yang, 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yanling, 2015	U	Y	U	U	Y	Y	Y	U	U
Yao et al, 2019	Y	Y	U	N	Y	Y	Y	Y	Y
Zhang, 2015	Y	Y	Y	U	Y	Y	Y	Y	Y

Y = Yes, N = No, U = Unclear, NA = Not applicable

1* The sample frame appropriate to address the target population
2* Criteria for sampled in an appropriate way
3* Adequate sample size
4* Study subjects and the setting described in detail
5* Analysis conducted with sufficient coverage of the identified sample
6* Outcomes measured in a valid way
7* Objective and standard criteria for measurement
8* Appropriate statistical analysis
9* Strategies for dealing with the response rate properly

6. Conclusão

No nosso conhecimento e pesquisa de literatura, este é o primeiro estudo que sumariza as medidas de prevalência mundial de ingestão insuficiente de iodo em gestantes. Os resultados permitem observar a prevalência mundial de ingestão insuficiente de iodo em gestantes de 53%, evidenciando que apesar do avanço nas políticas de erradicação dos distúrbios por deficiência de iodo por meio da fortificação do sal e do monitoramento periódico do estado nutricional de iodo da população em geral, em diferentes países, essa estratégias por si só pode não ser suficientes para garantir a ingestão adequada desse nutriente entre gestantes.

Verifica-se a necessidade do monitoramento do estado nutricional de iodo nesse grupo específico, a exemplo do que já é realizado em crianças na faixa etária escolar. Sugere-se que outras medidas, incluindo a suplementação pontual de iodo, possam ser tomadas para melhorar o cuidado clínico e nutricional de gestantes com o intuito de reduzir o risco de distúrbios por deficiência de iodo para o feto.

7. Considerações finais

Considerando a magnitude da prevalência mundial de ingestão insuficiente de iodo no grupo de gestantes do presente estudo, o risco de distúrbios por deficiência desse nutriente para o feto, como o cretinismo endêmico, aumenta durante esse período. Estudos como este podem estimar a dimensão do problema, além de indicar qual a região geográfica é mais afetada e onde está localizado o maior número de casos.

No nosso conhecimento, esta é a primeira revisão sistemática com metanálise de resultados de estudos sobre a prevalência da ingestão insuficiente de iodo em gestantes realizados em todos os continentes. Os resultados encontrados podem direcionar estratégias de atenção à saúde do grupo específico de gestantes e apontam para a necessidade do monitoramento e da construção e/ou reformulação de políticas específicas e direcionadas para tal fase da vida como por exemplo a política de suplementação que ainda não é estabelecida para gestantes em todos os países.

Quanto às limitações do presente estudo, destaca-se em alguns estudos a ausência de todos os dados necessários às análises. Os autores desses estudos foram contatados, porém não responderam às tentativas de contato. Quanto a análise realizada, foi observado viés de publicação e grande heterogeneidade entre os estudos. Para minimizar este resultado, foram realizadas análises de subgrupos e meta-regressão, porém os subgrupos ainda foram heterogêneos e a meta-regressão não foi capaz de identificar as fontes dessa heterogeneidade. No entanto, foi observado viés de publicação, sugerindo que os pequenos estudos podem ser fonte de distorção dos resultados.

Em resumo, diante do panorama atual da prevalência mundial de ingestão insuficiente de iodo no grupo de gestantes, medidas com enfoque na redução e controle são esperadas. Da mesma forma, mais estudos com rigor metodológico são necessários para ter resultados de maior confiabilidade e comparáveis.

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Apêndice 1 – *PRESS Guideline* — Search Submission & Peer Review Assessment
SEARCH SUBMISSION: THIS SECTION TO BE FILLED IN BY THE SEARCHER

Searcher: Érika Patriota; Isis Cristina; Nathalia Pizato; Vivian Siqueira; Sylvia Franceschini	**Email:** **vivian.goncalves@unb.br** **nathaliapizato@gmail.com**
Date submitted: 12/09/2019	**Date requested by:** 19/09/2019

Systematic Review Title:

The prevalence of insufficient iodine intake in pregnancy in worldwide: a systematic review.

This search strategy is:

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Database
(i.e., MEDLINE,CINAHL…):

MEDLINE

Interface

(i.e., Ovid, EBSCO, PUBMED…):

PUBMED

Research Question

(Describe the purpose of the search)

What is the prevalence of insufficient iodine intake among pregnant women?

PI(E)COS Format

(Outline the PICOs for your question — i.e., Patient, Index test, Reference standard, Outcome, and Study Design — as applicable)

P	Pregnant women from different regions of the world
I (E)	___
C	___
O	Prevalence of inadequate iodine nutritional status
S	Coss-sectional and cohort studies

Inclusion Criteria

(List criteria such as age groups, study designs, etc., to be included)

1	Studies with pregnant human
2	Data of prevalence of iodine insufficiency

3	We will include cross-sectional and cohort studies conducted on iodine deficiency among pregnant women in world.

Exclusion Criteria

(List criteria such as study designs, date limits, etc., to be excluded)

1	Studies investigating iodine status of pregnant women with known history thyroid diseases and/or other chronic diseases, pregnant women with iodine supplementation/radioiodine treatment and duplicate articles will be excluded from this review.
2	Animal studies, letters to editors, reviews, personal opinions, book chapters, commentaries, editorials and any publication without primary data.

Was a search filter applied?

Yes ( ) No (x)

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question]*

Other notes or comments you feel would be useful for the peer reviewer?

Please copy and paste your search strategy here, exactly as run, including the number of hits per line. *[mandatory]*

(Pregnancy OR Pregnancies OR Gestation OR Pregnant OR “Pregnant Women” OR “pregnant woman” OR “Prenatal Care” OR “Pregnancy in Adolescence” OR “Teen Pregnancy” OR “Teen Pregnancies” OR “Adolescent Pregnancy” OR “Adolescent Pregnancies”) AND (“Iodine deficiency” OR “Iodine insufficiency” OR “Iodine status” OR “Urinary Iodine Concentration” OR “serum iodine” OR iodine OR "iodine intake") AND (Prevalence OR Frequency OR Percentage OR Percent OR Proportion OR Ratio

OR Rate OR Percentage) AND (Survey OR “Cross-sectional studies” OR “Cross-sectional” OR Observational OR Cohort)

Total= 561 in PUBMED

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

Reviewer: Ana Claudia Morais Godoy Figueiredo	**Email:** **aninha_m_godoy@hotmail.com**
Date completed: 25/09/2019	

1. TRANSLATION

A ---No revisions	
B --- Revision(s) suggested	**x**
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

A estratégia de busca pode ser melhor estruturada conforme algumas recomendações para alteração da pergunta de investigação.

2. BOOLEAN AND PROXIMITY OPERATORS

A ---No revisions	**x**
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

3. SUBJECT HEADINGS

A ---No revisions	
B --- Revision(s) suggested	x
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

O termo "incidence" deve ser incluído na busca, bem como os tipos de estudo e todas as suas variações conforme descrito no MESH terms. Rever a necessidade dos termos relacionados com adolescência para não enviesar a sua seleção.

4. TEXT WORD SEARCHING

A ---No revisions	
B --- Revision(s) suggested	
C --- Revision(s) required	x

If "B" or "C," please provide an explanation or example:

Montar a estratégia de busca no modo avançado do PUBMED, uma vez que as aspas inseridas manualmente podem trazer resultados distorcidos. Desse modo, não é mais

recomendado construir as estratégias de busca em editor de texto, apenas no buscador da base de dados.

5. SPELLING, SYNTAX, AND LINE NUMBERS

A ---No revisions	
B --- Revision(s) suggested	
C --- Revision(s) required	**x**

If "B" or "C," please provide an explanation or example:

Descrever o número de artigos por linha da estratégia. Isso é um critério abordado no processo de avaliação do PRESS para que o leitor tenha maior clareza.

6. LIMITS AND FILTERS

A ---No revisions	
B --- Revision(s) suggested	**x**
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

Visando otimizar o tempo de trabalho, bem como tornar a estratégia mais sensível recomendo a utilização de filtros TIAB e MESH TERMS. Já foi comprovado por meio de estratégias validadas que esses filtros trazem benefícios na seleção de artigos relacionados com o tema.

OVERALL EVALUATION

(Note: If one or more “revision required” is noted above, the response below must be “revisions required”.)

A ---No revisions	
B --- Revision(s) suggested	
C --- Revision(s) required	

Additional comments:

Sugiro uma nova avaliação do PRESS após correções sugeridas, bem como a revisão dos itens descritos nos comentários.