Universidade Estadual Paulista
“Júlio de Mesquita Filho”
Faculdade de Medicina

Fernanda Bolfi

Associação das Concentrações de Iodo Urinário na Gestação com os Desfechos Maternos e Neonatais: Revisão Sistemática e Meta-Análise

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista “Júlio de Mesquita Filho”, Câmpus de Botucatu, para obtenção do título de Doutora em Fisiopatologia em Clínica Médica.

Orientadora: Profa. Dra. Vânia dos Santos Nunes Nogueira

Botucatu

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Epígrafe

"É Ele quem faz mudar os tempos e as circunstâncias; é Ele quem depõe os reis e os enaltece; é Ele quem dá sabedoria aos sábios e talento aos inteligentes"

Daniel 2:21

Dedicatória

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Resumo

Introdução: A concentração urinária de iodo é utilizada como indicador de deficiência de iodo em gestantes. Entretanto, não há evidência suficiente se esses resultados laboratoriais possuem relação com importantes desfechos maternos, neonatais e infantis. **Objetivo:** Este estudo buscou avaliar se baixos níveis de concentração urinária de iodo em gestantes, quando comparados a valores normais, estão associados a prejuízo nos desfechos maternos, neonatais e infantis. **Metodologia:** Foi realizada uma revisão sistemática de acordo com a metodologia do Joanna Briggs Institute (JBI), incluindo estudos observacionais em que gestantes com UIC < 150 μg/L foram comparadas com gestantes com UIC entre 150 μg/L e 249 μg/L. MEDLINE, EMBASE, LILACS, CENTRAL foram nossas bases de dados. Os desfechos maternos foram: aborto espontâneo, hipotireoidismo, hipotireoidismo subclínico, volume tireoidiano materno, valor médio do hormônio tireoestimulante (TSH); os desfechos neonatais foram: parto prematuro, natimorto, baixo peso ao nascer, pequeno para a idade gestacional, TSH neonatal elevado, comprimento ao nascer. O processo de seleção, avaliação de risco de viés e extração de dados foram realizados em pares e de forma independente. Para desfechos dicotômicos, o risco relativo (RR) com intervalo de confiança de 95% (IC) foi calculado como uma estimativa do efeito do iodo < 150 μg/L. O software STATA foi utilizado para realizar as meta-análises, utilizando o modelo randômico. A qualidade da evidência foi gerada de acordo com o sistema Grading of Recomendations Assessment, Development, and Evaluation (GRADE). **Resultados:** A estratégia de busca resultou em 6.472 artigos, dos quais 169 foram selecionados para leitura na íntegra e 57 foram incluídos nesta revisão. Não encontramos diferença entre UIC < 150 μg/L e UIC > 150 μg/L para os seguintes desfechos: aborto espontâneo (RR: 0,87, IC 95% 0,64 a 1,18, seis estudos, 4841 participantes, I2=0, baixa qualidade da evidência); hipotireoidismo materno (RR: 1,19, IC 95% 0,84 a 1,69, sete estudos, 11.371 participantes, I2=0); hipotireoidismo subclínico materno (RR: 1,05, IC 95% 0,87 a 1,26, 13 estudos, 14.705 participantes, I2=7,7%, baixa qualidade da evidência); volume tireoidiano materno (RR: -0,50, IC

95% −1,02 a 0,02, quatro estudos, 620 participantes, I2=0); medição do TSH materno (RR: −0,01, IC 95% −0,06 a 0,05, 21 estudos, 15.438 participantes, I2=51,2%, baixa qualidade da evidência); parto prematuro (RR: 1,18, IC 95% 0,94 a 1,47, 11 estudos, 15.098 participantes, I2=44,8%, qualidade de evidência muito baixa); natimorto (RR: 0,63, IC 95% 0,24 a 1,69, quatro estudos, 2.992 participantes, I2=13%, baixa qualidade de evidência); baixo peso ao nascer (RR: 1,08, IC 95% 0,86 a 1,36, nove estudos, 11.038 participantes, I2=37,2%, certeza de evidência muito baixa); pequeno para a idade gestacional (RR: 1,11, IC 95% 0,90 a 1,37, cinco estudos, 5230 participantes, I2=0); comprimento ao nascimento (RR: 0,13, IC 95% −0,12 a 0,37, cinco estudos, 4831 participantes, I2=64,4%) e TSH neonatal elevado (RR: 1,29, IC 95% 0,77 a 2,18, três estudos, 2233 participantes, I2= 52,2%). Os seguintes desfechos não puderam ser plotados na meta-análise: bócio neonatal, volume tireoidiano neonatal, morte infantil, malformações congênitas, desenvolvimento neuromotor e escores de QI. **Conclusão:** em gestantes, não encontramos associação entre UIC < 150 μg/L e desfechos maternos e neonatais, porém a qualidade da evidência da maioria dos resultados foi baixa ou muito baixa.

Abstract

Introduction: Urinary iodine concentration (UIC) is used as an indicator of iodine deficiency in pregnant women. However, there is no evidence synthesis showing whether these laboratory results are related to important maternal, neonatal and infant outcomes. **Objective:** to assess whether low levels of urinary iodine concentration in pregnant women are associated with impaired maternal and neonatal outcomes. **Methods:** A systematic review was performed according to the Joanna Briggs Institute (JBI) methodology, including observational studies in which pregnant women with UIC < 150 µg/L were compared to pregnant women with UIC between 150 µg/L and 249 µg/L. MEDLINE, EMBASE, LILACS, CENTRAL were our source databases. The maternal outcomes were spontaneous miscarriage, hypothyroidism, subclinical hypothyroidism, maternal thyroid volume, mean thyroid stimulating hormone (TSH) measurement; the neonatal outcomes were preterm birth, stillbirth, low birthweight, small for gestational age, neonatal elevated TSH, birth length. The selection process, risk of bias assessment and data extraction were performed in pairs and independently. For dichotomous outcomes, the relative risk (RR) with the 95% confidence interval (CI) was calculated as an estimate of the effect of iodine < 150 µg/L. The STATA software was used to perform the meta-analyses, using the random model. The quality of evidence was generated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. **Results:** The search strategy resulted in 6472 articles, of which 169 were selected for full reading and 57 were included in this review. We found no difference between UIC < 150 µg/L and UIC >150 µg/L for the following outcomes: miscarriage (RR: 0.87, IC 95% 0.64 to 1.18, six studies, 4841 participants, I2=0, low certainty of evidence); maternal hypothyroidism (RR: 1.19, IC 95% 0.84 to 1.69, seven studies, 11371 participants, I2=0); maternal subclinical hypothyroidism (RR: 1.05, IC 95% 0.87 to 1.26, 13 studies, 14705 participants, I2=7.7%, low certainty of evidence); maternal thyroid volume (RR: -0.50, IC 95% -1.02 to 0.02, four studies, 620 participants, I2=0); maternal TSH measurement (RR: -0.01, IC 95% -0.06 to 0.05, 21 studies, 15438

participants, I2=51.2%, low certainty of evidence); preterm birth (RR: 1.18, IC 95% 0.94 a 1.47, 11 studies, 15098 participants, I2=44.8%, very low certainty of evidence); stillbirth (RR: 0.63, IC 95% 0.24 to 1.69, four studies, 2992 participants, I2=13%, low certainty of evidence); low birth weight (RR: 1.08, IC 95% 0.86 to 1.36, nine studies, 11038 participants, I2=37.2%, very low certainty of evidence); small for gestational age (RR: 1.11, IC 95% 0.90 to 1.37, five studies, 5230 participants, I2=0); birth length (RR: 0.13, IC 95% -0.12 to 0.37, five studies, 4831 participants, I2=64.4%) and elevated neonatal TSH (RR: 1.29, IC 95% 0.77 to 2.18, three studies, 2233 participants, I2=52.2%). The following outcomes could not be plotted in a meta-analysis: neonatal goiter, neonatal thyroid volume, infant death, congenital malformations, neuromotor development and IQ scores. **Conclusion:** in pregnant women, we did not find an association between UIC < 150 μg/L and maternal and neonatal outcomes, however the certainty of evidence of most results were low or very low.

Introdução

O iodo é um micronutriente essencial para a vida. Esse mineral não é produzido pelo corpo humano, mas obtido por meio da alimentação e utilizado pela glândula tireoide para a produção dos hormônios tireoidianos, cujo processo acontece em etapas:

- captação de iodo: após a absorção no intestino delgado, o iodo passa para a corrente sanguínea e, na tireoide, a sua captação ocorre de modo ativo, realizado pelo cotransportador sódio/iodeto (NIS) presente na porção basal das células foliculares tireoidianas.
- oxidação do iodo: a proteína pendrina transporta o iodo da membrana basal até a membrana apical da célula folicular e então, ele é conduzido para o coloide, local em que sofre oxidação pela enzima tireoperoxidade (TPO);
- organificação: o iodo oxidado se liga a tireoglobulina (Tg) formando a monoiodotirosina (MIT) e a diiodotirosina (DIT);
- acoplamento: as moléculas de MIT e DIT se agrupam formando os hormônios tireoidianos. A ligação de duas DIT forma a tetraiodotironina (T4 ou tiroxina) e a junção de uma MIT com uma DIT forma a triiodotironina (T3);
- armazenamento, transporte e ação: os hormônios tireoidianos ficam armazenados no coloide e são liberados para a circulação pela membrana basal folicular. A maior parte deles é transportada ligada a proteínas plasmáticas, sendo a principal a globulina ligadora de tiroxina (TBG). O T3 é a forma ativa do hormônio tireoidiano, enquanto que o T4 é o principal hormônio liberado pela tireoide. A maior parte do T3 provém da conversão periférica de T4 em T3 que ocorre pela ação das enzimas deiodinases[1].

A regulação da função tireoidiana acontece pelo eixo hipotálamo-hipófise. O TRH (hormônio liberador da tireotrofina) é produzido pelo hipotálamo, que age na

adeno-hipófise e estimula a secreção do hormônio tireoestimulante (TSH) pelas células tireotróficas. O TSH fomenta todas as etapas de síntese dos hormônios tireoidianos. O T3 exerce retroalimentação negativa sobre a produção de TRH e TSH, preservando a homeostase hormonal [2].

A gestação induz algumas modificações fisiológicas na glândula tireoide materna. No primeiro trimestre, o hCG (gonadotrofina coriônica humana) se eleva. Como a subunidade α do TSH e do hCG são semelhantes, este promove uma atividade mimética estimuladora da tireoide, de intensidade leve, cursando com aumento da síntese dos hormônios tireoidianos e do volume da glândula. Durante a primeira metade da gestação até o termo, o hiperestrogenismo próprio do período tem como consequência a elevação da TBG, que também cursa com o aumento da produção de hormônio tireoidiano. Na segunda metade da gestação, a deiodinase do tipo 3, expressa na placenta, degrada o T4, o convertendo em T3 reverso. Com isso, as concentrações das frações livres do T3 e T4 tendem a diminuir e a do TSH sofrer discreta elevação [2,3].

Na primeira metade da gravidez, o feto é completamente dependente do fornecimento dos hormônios tireoidianos maternos. O T4 materno é transferido pela placenta até que a tireoide fetal esteja completamente desenvolvida, por volta de 18-20 semanas de gestação e o iodo da mãe é a única fonte desse nutriente para a síntese de hormônio tireoidiano do feto [2,3].

Portanto, para assegurar a disponibilidade adequada de hormônio tireoidiano materno e fetal em decorrência dessas adaptações fisiológicas transitórias da gestação, transcorre um aumento na produção materna de hormônio tireoidiano. Como consequência, as necessidades de iodo são acentuadamente mais elevadas na gestação [2,3].

A baixa ingestão de iodo pode resultar em depleção do estoque desse elemento e levar a produção inadequada de hormônios tireoidianos, que está associada a maior risco de desfechos adversos na gravidez, bem como para o bebê. Entre eles podemos

citar o parto prematuro (antes de 37 semanas), aborto, baixo peso (menor que 2500 g), mortalidade perinatal (óbitos ocorridos entre 22ª semana de gestação e o sexto dia completo de vida após o nascimento), pequeno para idade gestacional (recém-nascidos com peso menor ou igual ao percentil 10 para a idade gestacional), bócio, hipotireoidismo fetal, deficiência mental, elevada mortalidade neonatal (morte antes de 28 dias de vida completos) e infantil [2,4,5].

Diferente da maioria dos nutrientes dietéticos essenciais, o nível de iodo não está associado ao desenvolvimento socioeconômico, mas sim à localização geográfica [6]. Alguns alimentos contêm naturalmente esse nutriente, como peixes, frutos do mar, laticínios e vegetais plantados em solo com suficiência em iodo. No entanto, em muitos países, a dieta não é suficiente para fornecer as necessidades adequadas deste nutriente sem a fortificação do sal com iodo. Em 2020, 124 países tinham legislação para iodação obrigatória do sal e 21 tinham legislação que permitia a iodação voluntária. Como resultado, 88% da população global usa sal iodado. Apesar disso, mais de 1,8 bilhão de pessoas no mundo encontram-se em risco de deficiência de iodo por não atingir os níveis recomendados na alimentação. A falta deste elemento é um dos problemas de saúde mais graves em todo mundo, afetando todas as populações. No entanto, há grupos mais vulneráveis como as gestantes e as crianças [7].

Em condições de suficiência de iodo, mais de 90% deste elemento ingerido é excretado na urina, de modo que a concentração urinária de iodo (iodúria) é um bom indicador da ingestão recente de iodo ou de seu *status* em curto prazo. Na deficiência crônica de iodo, essa condição pode ser diagnosticada pela redução da sua excreção urinária (usualmente em 20%). A concentração urinária de iodo (UIC) pode ser expressa como concentração (µg/L), em relação à excreção urinária de creatinina (µg iodo/g creatinina), ou como excreção urinária de 24 horas (µg/dia). Para pesquisas populacionais ou estudos transversais, recomenda-se que a UIC seja medida em amostras de urina de uma amostra representativa do grupo alvo e expressa como a

mediana, em µg/L. A iodúria possui utilidade limitada na avaliação da ingestão ou *status* individual em função de variações amplas durante e entre os dias. Entretanto, tais variações são niveladas em amostras populacionais grandes, tornando a iodúria um indicador útil em nível populacional. A iodúria não é um indicador direto da função tireoidiana, porém valores baixos sugerem um maior risco para o desenvolvimento de disfunções tireoidianas [6,7].

Considerando os efeitos adversos da deficiência de iodo, em 2007, a Organização Mundial de Saúde (OMS), o Fundo das Nações Unidas para a Infância (UNICEF) e a *Global Iodine Network* [IGN, anteriormente conhecida como Conselho Internacional para Controle dos Distúrbios ou Deficiência de Iodo (ICCIDD)] propuseram um critério de avaliação para o índice nutricional de iodo nas gestantes e recomendaram a ingestão diária de 250 µg de iodo para gestantes e mulheres em período de lactação [8,9].

A deficiência de iodo ocorre quando a ingestão do elemento cai abaixo dos níveis recomendados. Para gestantes, a ingestão insuficiente de iodo é definida como o valor de iodúria abaixo de 150 µg/L. Valores entre 150 µg/L e 249 µg/L indicam ingestão adequada de iodo. Concentrações entre 250 µg/L e 499 µg/L sugerem consumo acima do requerido e valores iguais ou maiores que 500 µg/L, ingestão excessiva [8,9].

Apesar da concentração urinária de iodo ser utilizada como indicador de deficiência de iodo em gestantes, não há evidência suficiente se esses resultados laboratoriais possuem relação com importantes desfechos maternos, neonatais e infantis.

Objetivo

O presente estudo teve como objetivo avaliar se baixos níveis de concentração urinária de iodo em gestantes, quando comparados a valores normais, estão associados a prejuízo nos desfechos maternos ou neonatais.

Metodologia

Esta revisão sistemática foi realizada de acordo com a metodologia do *Joanna Briggs Institute* (JBI) para estudos de risco e etiologia [10], e o seu protocolo foi registrado na plataforma de registros de revisões sistemáticas PROSPERO (*International Prospective Register of Systematic Reviews*), que é uma base de registro de protocolos de revisões sistemáticas mantida pelo *Centre of Reviews and Dissemination* da Universidade de York e financiada pelo *National Institute for Health Research*. O código de registro na PROSPERO do nosso projeto é CRD42019110085. Tanto o protocolo como os resultados da revisão foram relatados de acordo com PRISMA (*Preferred reporting items for systematic review and meta-analysis*) [11].

CRITÉRIOS DE ELEGIBILIDADE

TIPOS DE ESTUDOS

Foram incluídos estudos de coorte prospectivos, retrospectivos e transversais analíticos (cross-sectional) nos quais gestantes com concentração urinária baixa de iodo foram comparadas a gestantes com concentração normal de iodo urinário.

Os estudos incluídos seguiram a estrutura PECO (P: Participantes, E: Exposição, C: Comparação, O: Desfechos) descrita abaixo:

- **Participantes (P):** As participantes são mulheres gestantes, gestação única, com idade entre 16 e 45 anos, moradoras de regiões com oferta normal ou deficiência leve/moderada de iodo, sem restrições étnicas, sem história de doenças da tireoide ou outras doenças crônicas.
- **Exposição (E)**: O grupo de exposição é o com deficiência de iodo. Consideramos deficiência de iodo como concentração urinária de iodo média menor que 150 µg/L.

- **Comparação (C)**: O grupo de comparação é o com suficiência de iodo. Consideramos a suficiência de iodo como concentração urinária de iodo média entre 150–249 µg/L.
- **Desfechos (O)**:

Maternos: aborto espontâneo, hipotireoidismo franco e hipotireoidismo subclínico (na gravidez), presença de bócio, volume tireoidiano, média do valor do TSH.

Neonatais/infantis: prematuridade (nascimento com menos de 37 semanas de gestação), natimorto, baixo peso ao nascer (menos de 2.500 g), pequeno para a idade gestacional (peso menor ou igual ao percentil 10 para sua idade gestacional), hipotireoidismo neonatal ou TSH elevado, comprimento ao nascer, anomalias congênitas (incluindo cretinismo), bócio neonatal, volume tireoidiano neonatal, morte infantil (óbito no primeiro ano de vida), desenvolvimento neuro motor e escore de coeficiente de inteligência.

Métodos de Pesquisa para Identificação de Estudos

Base de Dados Eletrônica

Quatro estratégias gerais e adaptativas de pesquisa foram criadas para as seguintes bases de dados de saúde eletrônicas: *Embase* (por *Elsevier*, 1980–2020), *Medline* (por *Pubmed*, 1966- 2020), *LILACS* (por *Virtual Health Library*, 1982–2020) e Registro de Estudos Clínicos Controlados da Colaboração Cochrane (*CENTRAL – Cochrane*). Nas plataformas *Medline* e *Embase*, utilizamos o filtro para estudos randomizados da *Cochrane*. Os termos relacionados e sinônimos de gravidez e iodo urinário foram utilizados. Não houve restrição de idioma ou data de publicação. As bases de dados foram pesquisadas em 07 de novembro de 2019 e atualizadas em 06 de julho de 2022.

Os estudos elegíveis também foram pesquisados no SCOPUS, *Web of Science* e *Allied Nursing and Health Literature Cumulative Index* (CINAHL).

O software de gerenciamento de citações EndNote X9 foi usado para baixar as referências e remover entradas duplicadas. A triagem inicial de resumos e títulos foi realizada por meio do aplicativo da web gratuito Rayyan QCRI. As estratégias de pesquisa mencionadas encontram-se descritas nas Informações de Apoio (SI -S1) [12].

Seleção de Estudos e Extração de Dados

Dois revisores (FB e MBM) selecionaram independentemente os títulos e resumos identificados durante a busca na literatura. Os estudos potencialmente elegíveis para inclusão na revisão foram lidos na íntegra e, posteriormente, avaliados em termos de adequação usando a estrutura PECO proposta. Sempre que houve discordância no processo de seleção, foi alcançado um consenso por meio de discussão com o coordenador do projeto (VSNN).

Para os estudos selecionados para inclusão, ambos os revisores utilizaram um formulário de extração padronizado, para cada estudo selecionado, a fim de que todas as informações referentes a cada estudo pudessem ser computadas: o ano de publicação, desenho do estudo, número de gestantes incluídas, média de idade materna, trimestre da gestação, país do estudo, período em que o estudo foi realizado, status de iodo na região, fatores confundidores descritos no estudo, critérios de elegibilidade (características da população estudada, valores utilizados como os critérios de exposição e controle), inclusão de gestantes com anticorpo tireoidiano positivo, tipos de desfechos analisados em cada estudo, correção do iodo urinário pela creatinina excretada, se o estudo foi incluído na meta-análise.

Para garantir a consistência entre os revisores, conduzimos um exercício de calibração antes do início da revisão.

No caso de publicações duplicadas ou de mais relatos do estudo primário, a extração foi otimizada por meio do uso da melhor informação disponível para todos

os itens do mesmo estudo. Um debate entre os revisores e VSNN foi realizado no caso de desacordos entre os revisores nesse processo.

Para cada estudo selecionado, o risco de viés foi avaliado, de acordo com a ferramenta de risco de viés JBI, revisada para estudos de etiologia e risco. Utilizamos instrumentos específicos para estudos transversais e de coorte [10]. Cada um dos itens foi avaliado em pares e de forma independente por três revisores (FB, MBM, SESF) para inclusão ou exclusão do estudo.

Síntese e Análise de Dados

Os dados publicados nos estudos incluídos foram a unidade de análise e, utilizamos preferencialmente, os dados de análise por intenção de tratar. Resultados semelhantes foram plotados na meta-análise usando Stata Statistical Software 16 (Stata Statistical Software: Release 16. College Station, TX, StataCorp LLC, EUA). Escolhemos o modelo de efeitos aleatórios como modelo analítico na meta-análise.

Estimativa do Efeito da Exposição

Para dados contínuos, os valores pós-intervenção foram transformados em diferença de médias (MD) entre os grupos mais intervalos de confiança de 95% (IC). Quando a diferença de médias ajustada (MADs) estava disponível, preferimos usá-las. As MDs e MADS foram incluídas na meta-análise usando o método genérico do inverso da variância. Para estudos que relataram mediana e intervalo interquartil, a média estimada da amostra e o desvio padrão (DP) foram obtidos de Hozo et al [13, 14]. Para desfechos dicotômicos, o risco relativo (RR) com o IC de 95% foi calculado como uma estimativa do efeito da UIC < 150 µg/L.

Lidando com Dados Ausentes

Os autores dos estudos originais foram contatados, caso necessário, para obtenção de informações ausentes de cada estudo incluído. Nós utilizamos apenas os dados disponíveis (nos artigos publicados ou fornecidos por contato de autores). Não utilizamos nenhum método para colocar os dados ausentes. Quando disponível, usamos preferencialmente dados de análises por intenção de tratar.

Avaliação da heterogeneidade estatística

A inconsistência entre os resultados dos estudos incluídos foi apurada pela inspeção visual do gráfico em floresta (sem sobreposição dos ICs sobre a estimativa de efeito dos estudos individuais) e pela estatística de Higgins ou I^2, no qual $I^2 > 50\%$ indica uma probabilidade moderada de heterogeneidade e pelo teste qui-quadrado (Chi^2), onde $p < 0{,}10$ indicou heterogeneidade [14].

O intervalo de predição (PI) foi calculado para a meta-análise de efeito aleatório, se Chi^2 $p < 0{,}1$ ou $I^2 > 35\%$ e mais de cinco estudos. PI prevê o possível efeito do tratamento em um cenário de estudo individual, enquanto a meta-análise de efeito aleatório resume o efeito médio entre os estudos. Como o efeito potencial do tratamento, quando aplicado em um cenário de estudo individual, pode diferir do efeito médio, o PI fornece informações interessantes para a prática clínica [14].

Avaliação do viés de publicação

Para um desfecho específico, quando mais de 10 estudos foram incluídos na meta-análise, usamos o gráfico de funil e o teste de regressão de Egger para investigar a presença de viés de publicação [15].

Análise de Sensibilidade

As análises de sensibilidade foram realizadas comparando estudos de acordo com dados publicados versus dados imputados e comparando o grupo de UIC entre 150-249 µg/L versus UIC > 150 µg/L.

Qualidade da evidência

GRADE

A qualidade da evidência do efeito estimado da intervenção para os desfechos que podem ser plotados na meta-análise foram geradas de acordo com o sistema *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE). O GRADE avalia a qualidade da totalidade da evidência de certa tecnologia na saúde sobre um desfecho, especificamente, os desfechos mais importantes da perspectiva do paciente. Estudos randomizados possuem a melhor qualidade de evidência, porém a qualidade é deteriorada se os estudos apresentarem grandes limitações que possam interferir nas estimativas dos efeitos de tratamento. Essas limitações incluem o risco de viés, inconsistência de resultados, evidência indireta, imprecisão e viés de relato. Por outro lado, estudos observacionais são iniciados com baixa qualidade de evidência. No entanto, a qualidade da evidência pode aumentar quando os estudos apresentam rigorosamente um dos seguintes critérios: a magnitude do efeito do tratamento é muito grande, há evidência de uma relação dose-resposta ou todos os vieses plausíveis diminuiriam a magnitude do efeito do tratamento [16].

Referências

1. Vaisman M, Rosenthal D, Carvalho DP. Enzymes involved in thyroid iodide organification. Endocrinol Metabol 2004;48(1):9-15; doi: 10.1590/s0004-27302004000100003.
2. Burrow GN, Fischer DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994;331(16):1072-1078; doi: 10.1056/NEJM199410203311608.
3. Korevaar TIM, Medici M, Visser TJ, et al. Thyroid Disease in Pregnancy: New Insights in Diagnosis and Clinical Management. Nat Rev Endocrinol 2017;13(10):610–622; doi: 10.1038/nrendo.2017.93.
4. Nazarpour S, Ramezani Tehrani F, Amiri M, et al. Maternal Urinary Iodine Concentration and Pregnancy Outcomes: Tehran Thyroid and Pregnancy Study. Biol Trace Elem Res 2020;194(2):348–359; doi: 10.1007/s12011-019-01812-5.
5. Glinoer D. The Regulation of Thyroid Function in Pregnancy: Pathways of Endocrine Adaptation from Physiology to Pathology. Endocr Rev 1997;18(3):404-433; doi: 10.1210/edrv.18.3.0300.
6. Rohner F, Zimmermann M, Jooste P, et al. Biomarkers of Nutrition for Development-Iodine Review. Journal of Nutrition 2014;144(8); doi: 10.3945/jn.113.181974.
7. Zimmermann MB, Andersson M. Global Perspectives in Endocrinology: Coverage of Iodized Salt Programs and Iodine Status in 2020. Eur J Endocrinol 2021;185(1): R13–R21; doi: 10.1530/EJE-21-0171.
8. World Health Organization, United Nations Children’s Fund, International Council for the Control of Iodine Deficiency Disorders. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers, 3rd edn. Geneva: World Health Organization. 2007
9. Andersson M, de Benoist B, Delange F, et al. Prevention and Control of Iodine Deficiency in Pregnant and Lactating Women and in Children Less than 2-Years-Old: Conclusions and Recommendations of the Technical Consultation. In: Public Health Nutrition Cambridge University Press; 2007; pp. 1606–1611; doi: 10.1017/S1368980007361004.
10. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. In: Joanna Briggs Institute Reviewer's Manual. (Aromataris E, Munn Z. eds.).

The Joanna Briggs Institute: 2017. Available from https://reviewersmanual.joannabriggs.org/.

11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. J Clin Epidemiol 2009;62(10):e1-34; doi: 10.1016/j.jclinepi.2009.06.006.
12. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a Web and Mobile App for Systematic Reviews. Syst Rev 2016;5(1); doi: 10.1186/s13643-016-0384-4.
13. Hozo SP, Djulbegovic B, Hozo I. Estimating the Mean and Variance from the Median, Range, and the Size of a Sample. BMC Med Res Methodol 2005;5; doi: 10.1186/1471-2288-5-13.
14. Riley RD, Higgins JP, Deeks JJ. Interpretation of Random Effects Meta-Analyses. BMJ 2011;342:d549; doi: 10.1136/bmj.d549.
15. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Intervention. Second. Chichester (UK): John Wiley & Sons; 2019.
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-926; doi: 10.1136/bmj.39489.470347.AD.

Artigo

ASSOCIATION OF URINARY IODINE CONCENTRATIONS IN PREGNANCY WITH MATERNAL AND NEWBORN OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Fernanda Bolfi[1], Maryan Borcsik Marum[1], Samantha Ellen da Silva Fonseca[1], Glaucia Maria Ferreira da Silva Mazeto[1], Celia Regina Nogueira de Camargo[1] and Vania dos Santos Nunes-Nogueira[1]

[1] Department of Internal Medicine, São Paulo State University (UNESP), Medical School, Botucatu, Sao Paulo, Brazil

Corresponding Author:

Vania dos Santos Nunes Nogueira

Departamento de Clínica Médica–FMB–UNESP

Avenida Professor Mário Rubens Guimarães Montenegro s/n, Bairro UNESP, Campus Botucatu, Botucatu-SP, Brazil

Zip Code: 18618-687

Tel: (55 14) 3880 11 71

Fax: (55 14) 3880 16 67

E-mail: vania.nunes-nogueira@unesp.br

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Abstract

Introduction: Urinary iodine concentration (UIC) is used as an indicator of iodine deficiency in pregnant women. However, there is no evidence synthesis showing whether these laboratory results are related to important maternal, neonatal and infant outcomes. **Objective:** to assess whether low levels of urinary iodine concentration in pregnant women are associated with impaired maternal and neonatal outcomes. **Methods:** A systematic review was performed according to the Joanna Briggs Institute (JBI) methodology, including observational studies in which pregnant women with UIC < 150 µg/L were compared to pregnant women with UIC between 150 µg/L and 249 µg/L. MEDLINE, EMBASE, LILACS, CENTRAL were our source databases. The maternal outcomes were spontaneous miscarriage, hypothyroidism, subclinical hypothyroidism, maternal thyroid volume, mean thyroid stimulating hormone (TSH) measurement; the neonatal outcomes were preterm birth, stillbirth, low birthweight, small for gestational age, neonatal elevated TSH, birth length. The selection process, risk of bias assessment and data extraction were performed in pairs and independently. For dichotomous outcomes, the relative risk (RR) with the 95% confidence interval (CI) was calculated as an estimate of the effect of iodine < 150 µg/L. The STATA software was used to perform the meta-analyses, using the random model. The quality of evidence was generated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. **Results:** The search strategy resulted in 6472 articles, of which 169 were selected for full reading and 57 were included in this review. We found no difference between UIC < 150 µg/L and UIC >150 µg/L for the following outcomes: miscarriage (RR: 0.87, IC 95% 0.64 to 1.18, six studies, 4841 participants, I^2=0, low certainty of evidence); maternal hypothyroidism (RR: 1.19, IC 95% 0.84 to 1.69, seven studies, 11371 participants, I^2=0); maternal subclinical hypothyroidism (RR: 1.05, IC 95% 0.87 to 1.26, 13 studies, 14705 participants, I^2=7.7%, low certainty of evidence); maternal

thyroid volume (RR: -0.50, IC 95% -1.02 to 0.02, four studies, 620 participants, I^2=0); maternal TSH measurement (RR: -0.01, IC 95% -0.06 to 0.05, 21 studies, 15438 participants, I^2=51.2%, low certainty of evidence); preterm birth (RR: 1.18, IC 95% 0.94 a 1.47, 11 studies, 15098 participants, I^2=44.8%, very low certainty of evidence); stillbirth (RR: 0.63, IC 95% 0.24 to 1.69, four studies, 2992 participants, I^2=13%, low certainty of evidence); low birth weight (RR: 1.08, IC 95% 0.86 to 1.36, nine studies, 11038 participants, I^2=37.2%, very low certainty of evidence); small for gestational age (RR: 1.11, IC 95% 0.90 to 1.37, five studies, 5230 participants, I^2=0); birth length (RR: 0.13, IC 95% -0.12 to 0.37, five studies, 4831 participants, I^2=64.4%) and elevated neonatal TSH (RR: 1.29, IC 95% 0.77 to 2.18, three studies, 2233 participants, I^2=52.2%). The following outcomes could not be plotted in a meta-analysis: neonatal goiter, neonatal thyroid volume, infant death, congenital malformations, neuromotor development and IQ scores. **Conclusion:** in pregnant women, we did not find an association between UIC < 150 µg/L and maternal and neonatal outcomes, however the certainty of evidence of most results were low or very low.

Introduction

Iodine is the most important micronutrient for the thyroid hormone synthesis, that is an essential component of thyroxine (T4) and triiodothyronine (T3), and it must be provided in the diet [1,2]. Unlike most other essential dietary nutrients, iodine status is not linked to socioeconomic development but rather to geography [3].

Some foods naturally contain this nutrient as fish, seafood, dairy products, and vegetables grown in iodine-sufficient soil or those that are added as salt but despite this, over 1.8 billion people worldwide are at risk of iodine deficiency because do not get enough iodine in their diet. Inadequate iodine intake leads to inadequate thyroid hormone production and the consequences of hypothyroidism [2].

The maternal iodine is the only source of iodine for fetal thyroid hormone synthesis. Pregnant women are susceptible to iodine deficiency due to increased renal clearance and additional fetal requirements. Thereby consuming an adequate amount of iodine during pregnancy is important for fetal development [4].

When severe iodine deficiency occurs during pregnancy, it is associated with fetal hypothyroidism, mental impairment, goiter, increased neonatal mortality [5].

In conditions of iodine sufficiency, over 90% of ingested iodine is excreted in the urine, making urinary iodine concentration (UIC) a good indicator of recent iodine intake, or short-term iodine status. In chronic iodine deficiency this condition can be diagnosed by UIC excretion reduction (usually 20%) [6].

Considering the adverse effects of iodine deficiency, in 2007, the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the Global Iodine Network [IGN, formerly known as the International Council for Control of Disorders or Iodine Deficiency (ICCIDD)] proposed an evaluation criterion for the nutritional index of iodine in pregnant women and recommended a daily intake of 250 µg of iodine for pregnant and lactating women [6].

Iodine deficiency occurs when iodine intake falls below recommended levels. For pregnant women, insufficient iodine intake is defined as a UIC below 150 µg/L. Values between 150 µg/L and 249 µg/L indicate adequate iodine intake. Concentrations between 250 µg/L and 499 µg/L suggest consumption above the required and values equal to or greater than 500 µg/L, excessive intake [6].

The UIC has limited utility in assessing individual intake or status because of large variations within and between days. Conversely, these variations level out in large population samples though, making UIC a useful population-level indicator. UIC is not a direct indicator of thyroid function, but low values suggest a greater risk of developing thyroid disorders [6].

Despite the UIC have been used as indicator of iodine deficiency in pregnant women, there is no enough evidence if these laboratorial results have relationship with important maternal, neonatal and infant outcomes.

Methods

This systematic review was conducted according to the Joanna Briggs Institute (JBI) methodology and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Studies selection process, risk of bias assessment and data extraction were performed in pairs and independently. STATA software was used for the meta-analysis. Its protocol was registered in the International Prospective Register of Systematic Reviews under CRD42019110085 [7,8].

Eligibility criteria

We included observational studies in which the levels of UIC in pregnant women were analyzed and if these laboratorial results have relationship with important maternal, neonatal and infant outcomes and that meet the “PECO” structure described below.

Participants (P)

We considered pregnant women, aged 16-45 years, single pregnancy, living in region with normal iodine supply, without ethnicity restrictions or history of thyroid diseases or other chronic diseases.

Exposition (E)

The exposition group was the iodine deficiency; we considered iodine deficiency as median UIC less than 150 µg/L.

Comparison (C)

The comparison group was the iodine sufficiency, we considered iodine sufficiency as median UIC between 150-249 µg/L.

Outcomes (O)

The maternal outcomes analyzed were spontaneous miscarriage, hypothyroidism and subclinical hypothyroidism (in pregnancy), goiter, thyroid volume, mean TSH measurement.

The neonatal/infant outcomes analyzed were preterm birth, stillbirth, low birthweight (less than 2500 g), small for gestational age (birth weight of less than 10th percentile for gestational age), neonatal hypothyroidism or elevated TSH, birth length, congenital malformations (including cretinism), neonatal goiter, neonatal thyroid volume, infant death (death in the first year of life), neuro and motor development, intelligence quotient (IQ) scores.

Identification of studies

Electronic databases

General research strategies were created for the following electronic health databases: Embase (by Elsevier), MEDLINE (by PubMed), LILACS (by Virtual Health Library), and Registry of Controlled Clinical Studies of the Cochrane Collaboration (CENTRAL–Cochrane). Eligible studies were also surveyed in the SCOPUS, Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

There were no restrictions on language or year of publication. Databases were searched on November 07, 2019 and updated on July 06, 2022. The Medical Subject Headings that were used included: “pregnant women”, “urinary iodine”, “iodine deficiency” and “hypothyroidism”. The search strategies for the primary databases are included in the Supporting Information (S1).

EndNote X9 citation management software was used to download the references and remove duplicate entries. The initial screening of abstracts and titles was performed using the free web application Rayyan QCRI [9].

Study selection and data extraction

Two reviewers (FB and MBM) independently selected the titles and abstracts identified during the literature search. Potentially eligible studies for inclusion in the review were read completely and subsequently assessed in terms of the appropriateness using the proposed PECO structure. Whenever there was disagreement in the selection process, a consensus was reached through discussion with the project coordinator (VSNN).

For the studies selected for inclusion, both reviewers used a standardized extraction form so that all information regarding each study could be computed.

Assessment of risk of bias in included studies

For the outcomes from each selected study was assessed according to the revised JBI risk-of-bias tool for etiology and risk studies. We used specific instruments for cross-sectional and cohort studies[7]. Each of the items was evaluated in pairs and independently by three reviewers (FB, MBM, SESF) to include or exclude the study.

Synthesis and data analysis

The unit of analysis was the data published in the included studies, and we preferentially used data from intention-to-treat analysis. Similar outcomes were plotted in the meta-analysis using Stata Statistical Software 16 (Stata Statistical Software: Release 16. College Station, TX, StataCorp LLC, USA). We chose the random effects model as the analytic model in the meta-analysis.

Estimate of exposure effect

For continuous data, the post-intervention values were transformed into mean differences (MD) between the groups plus 95% confidence intervals (CI). When mean adjusted differences from change score (MADs) were available, we preferred to use them. The MDs and MADS were included in the meta-analysis using the generic inverse-variance method. For studies that reported median and interquartile range, the estimated means of the sample and standard deviation (SD) were obtained from Hozo et al. [10,11].

For dichotomous outcomes, the relative risk (RR) with the 95% CI was calculated as an estimate of the effect of UIC < 150 µg/L.

Assessment of publication biases

When more than 10 studies were included in the meta-analysis, we used a funnel plot and Egger regression test to investigate the presence of publication bias [12].

Assessment of statistical heterogeneity

Inconsistencies between the results of the studies included were ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies) and by Higgins or I^2 statistic, in which $I^2 > 50\%$ indicated a moderate probability of heterogeneity, and by chi-squared tests (Chi^2), where $p < 0.10$ indicated heterogeneity[11] .

Prediction interval (PI) was calculated for the random effect meta-analysis, if Chi^2 $p < 0.1$ or $I^2 > 35\%$ and more than five studies. PI predicts the possible treatment effect in an individual study setting, whereas the random effect meta-analysis summarizes the average effect across the studies. Because the potential treatment effect when applied within an individual study setting may differ from the average effect, the PI provides interesting insights for clinical practice[11].

Sensitivity analysis

The sensitivity analyses were performed by comparing studies according to published vs imputed data, and by comparing comparison group as median urinary iodine concentration (UIC) between 150-249 µg/L vs UIC > 150 µg/L.

Quality of the evidence

The quality of evidence for estimating the effect of exposure on outcomes that could be plotted in the meta-analysis was generated in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. GRADE is a structured process for rating the quality of evidence in systematic reviews or in guidelines for health care. Randomized controlled trials begin as high-quality evidence; however, the confidence in the evidence may decrease if the studies have major limitations that may interfere with the estimates of the treatment effect. These limitations include the risk of bias, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. Conversely, observational studies are initiated with a low certainty of evidence. However, the quality of evidence can increase when studies rigorously present one of the following criteria: the magnitude of the treatment effect is very large, there is evidence of a dose–response relationship, or all plausible biases would decrease the magnitude of the treatment effect [13].

Results

Selection of studies

The search strategies yielded different studies, and after removing duplicates, 6472 studies remained. Four articles with manual searches were included [14–17]. We selected 169 studies that had a high probability of meeting our inclusion criteria for a complete examination (Figure 1). After completely examining these references, 57 studies met our eligibility criteria [1,14–69]. A total of 112 articles were excluded from the final examination for the following reasons: six by the type of study

design, one was a research protocol, 42 did not correlate UIC with outcomes, 34 demonstrated lack of division between sufficiency/deficiency in the correlation of UIC and outcomes, 29 were not in agreement with the PECO structure (the references from studies not included are on Supporting Information – S2). In the meta-analysis, 41 studies were included and a total of 16 studies were excluded from the meta-analysis for the following reasons: two had different references for the same study [22,59], five had missing data [25,33,47,48,60]. Other two studies had different instruments for evaluating the same outcome [21,69], both evaluated maternal goiter, although one evaluated by ultrasound [69] and the other by thyroid palpation [21], considering there was a great disparity between their results, no meta-analysis was performed. Regarding neuromotor development and IQ scores, nine studies [27,29,38,41,45,50,52,62,68] evaluated the relationship between UIC and these outcomes.

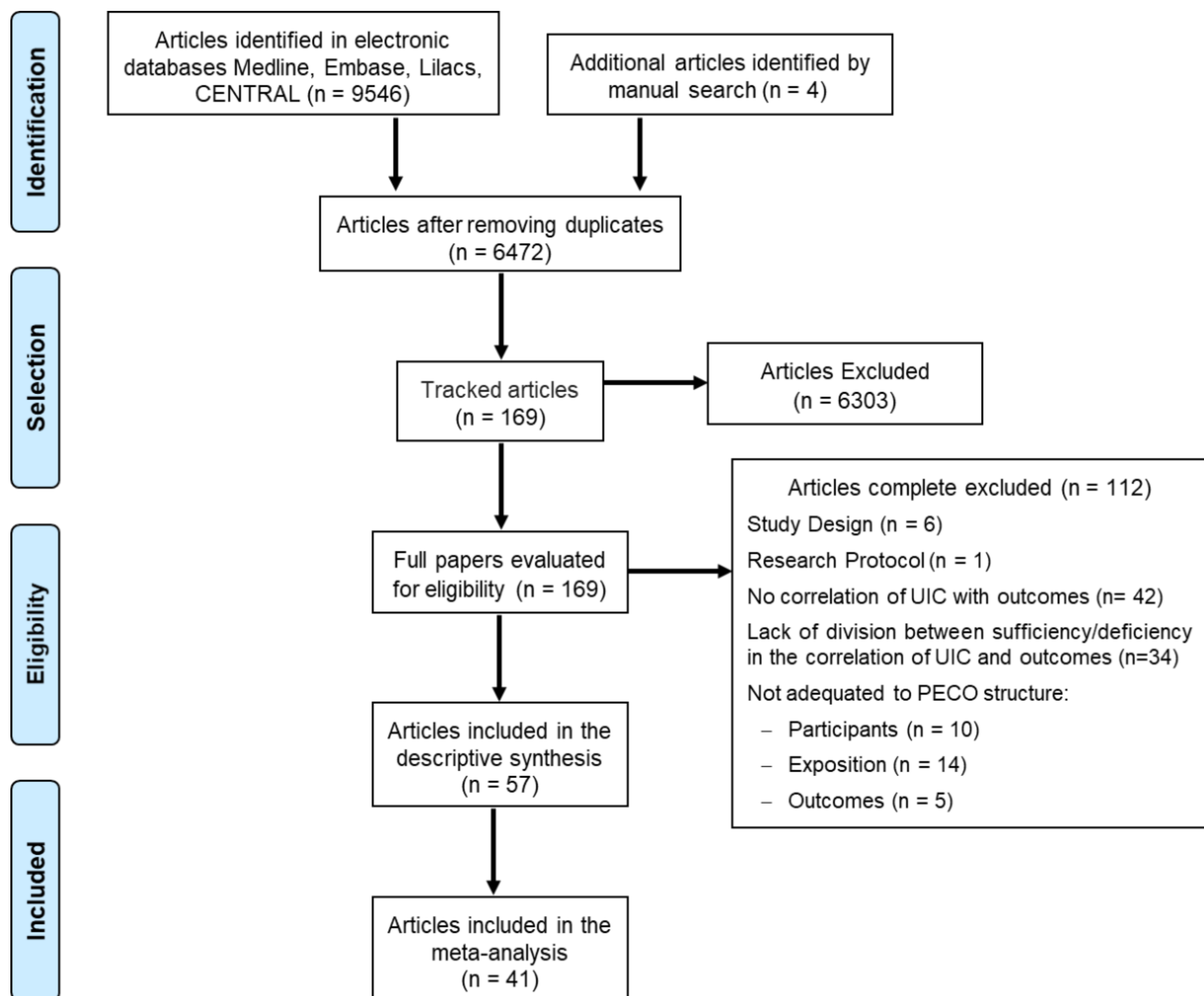

Figure 1. Flow diagram of selected studies

Study Characteristics

Evaluating the included studies, it was possible to verify that all outcomes analyzed were dichotomous, with the exception of the maternal TSH measurement, that was continuous. Regarding the types of studies, 58% were cohort and 42% were cross-sectional. Population ranged from 35 to 6128 pregnant women. The three gestational trimesters were included. The regions are divided: 42% from Asia, 30% from Europe, 7% from Eurasia, 9 % from South America, 3,5% from Africa and North America, 5% from Australia.

The data regarding the main characteristics of each study are presented in Table 1.

Table 1. Characteristics and summary of findings of 57 included studies that investigated associations of UIC in pregnancy with maternal and newborn outcomes

Study	Year	Study Design	Pregnant women (n)	Mean Age (Years)	Gestational Trimester	Country	Period	Iodine Status	Confounders	Participants	Exposition (UIC µg/L)	Control (UIC µg/L)	Thyroid Antibody	Outcomes	correction by creatinine	Inclusion in meta-analysis
Abel	2018	Cross-sectional	816	30	2nd	Norway	1999 to 2008	Mild to moderate deficiency	Maternal age, education, parity, pre-pregnancy BMI, fiber intake, smoking in pregnancy, plasma ferritin, whole blood selenium, and gestational age	Pregnant women, non-supplement users	100 - 150	≥150	Yes	TSH	Yes	Yes
Berg	2017	Cohort	197	32	2nd	Norway	2007 to 2009	Mild to moderate deficiency	Maternal age, education, parity, pre-pregnancy BMI, smoking in pregnancy, intake of dairy products/marine food/eggs, dietary intake of iodine, gestational age	Pregnant women with no prior thyroid-related disease	< 150	≥150	Yes	TSH	Yes	Yes
Chen	2018	Cohort	1140	28	2nd, 3rd	China	2014 to 2016	Sufficient	Maternal age, ethnic group, alcohol consumption, smoking, average personal income, folic acid supplementation, vitamin or mineral supplementation, abortion history, parity, morning sickness, educational level, maternal height, BMI	Pregnant women with no severe illnesses	<150	150–249	No	Birth length	Yes	Yes
Gyamfi	2018	Cross-sectional	186	28	1st, 2nd, 3rd	Gana	January to April 2016	Sufficient	History of thyroid disease, thyroid medication, thyroidectomy, smoking	Pregnant women, any trimester	< 150	150–249	No	Thyroid volume (> or < 18 mL)	No	No, different instrument analysis
Hynes	2017	Cohort	311	29	2nd, 3rd	Australia	1999 to 2001	Mild deficiency	Gestational age at UI collection, maternal age, gestational length, birth weight and sex, maternal education	Pregnant women	<150	≥150	NR	Performance in literacy and numeracy; language disorders	No	No, same population Hynes 2013
Kianpour	2019	Cohort	388	29	1st, 2nd	Iran	NR	Sufficient	Demographic characteristics, obstetrics' history (the number of pregnancies, miscarriages, and deliveries, infertility, preterm delivery and complications of previous pregnancy), history of autoimmune diseases, diabetes mellitus and thyroid dysfunction	Single gestation, no clinical autoimmune diseases, acute or chronic diseases and known thyroid disease	<150	>150	Yes	Miscarriage	Yes	Yes
Koyuncu	2018	Cross-sectional	431	28	1st	Turkey	January to July 2016	Sufficient	NR	Pregnant women without thyroid medication or thyroid diseases	<150	150 - 249	NR	TSH	No	Yes
Levie	2019	Cohort	1826	30	1st	Sweden	2007 to 2010	Mild to moderate deficiency	Gestational age, hCG maternal age, maternal ethnicity, maternal educational level, parity, maternal BMI, smoking status, child sex, TPOAb	Pregnant women, TPOAb negative	<150	150 - 249	Yes	TSH range	Yes	No, missing data
Markhus	2018	Cohort	851	NR	2nd	Norway	2011 to 2014	Mild to moderate deficiency	Age, pre-pregnancy weight and height, parity, education, marital status, use of iodine containing supplements, use of omega-3 supplements in pregnancy, daily smoking in pregnancy	Singleton pregnancy, no thyroid medication in pregnancy, and no severe genetic disorder	<150	>150	NR	Child neurodevelopment at 6, 12 and 18 months	Yes	No, descriptive analysis
Mioto	2018	Cross-sectional	78	28	1st	Brazil	2012 to 2016	Sufficient	NR	Pregnant women, no previous thyroid disease, no iodine supplementation, negative TPOAb and TgAb	< 150	150 - 249	No	TSH, thyroid volume	Yes	Yes
Murcia	2017	Cohort	522	30	1st	Spain	2009 to 2013	Sufficient/Mild deficiency	Maternal characteristics: country of origin, educational level, social class, cohabitant, employed at baby's age 1 year, smoking, history of thyroid disease, age. Infant characteristics: sex, breastfeeding, day-care center attendance. Perinatal outcomes: fetal growth restriction	Pregnant women	< 150	150-249	No	Mental Development Index, Psychomotor Development Index	No	No, descriptive analysis
Nazarpour	2019	Cohort	1044	27	1st, 2nd, 3rd	Iran	2013 to 2016	Sufficient	Age, BMI, TPOAb	Pregnant women with no consume iodine-containing supplement	< 150	150-249	Yes	TSH, miscarriage, stillbirth/fetal death, birth lenght	No	Yes
Pan	2019	Cross-sectional	890	28	1st, 2nd, 3rd	China	2016 to 2017	Sufficient	Age, height, weight, trimester	18-44-year old pregnant women	<150	150-249	Yes	TSH	Yes	Yes
Ruiz Ochoa	2017	Cohort	70	31	1st	Spain	NR	Sufficient	Parity, history of miscarriage, iodized salt, pharmacological supplements	Healthy pregnant women with normal thyroid function and negative thyroid immune findings	< 150	150-249	No	TSH	No	Yes
Torlinska	2018	Cohort	2597	29	1st, 2nd, 3rd	United Kingdom	1991 to 1992	Mild deficiency	Mother's BMI (pre-pregnancy), age, parity, cigarette smoking during early pregnancy and trimester	Singleton pregnancy	< 150	150-249	Yes	Preterm, small for gestational age	Yes	Yes
Ulu	2017	Cross-sectional	180	26	3rd	Turkey	July to september 2011	Mild to moderate deficiency	Smoking in pregnancy, iodized salt consumption	Pregnant women, aged between 16-40 years. No use iodine supplements or thyroid hormone replacement, no history of hypothyroidism	< 150	150-249	No	TSH	No	No, missing data
Xiao	2017	Cohort	1255	28	1st	China	2012 to 2014	Sufficient	BMI, abdominal circumference, blood pressure, heart rate, smoking rate, drinking rate, TSH, FT4, TPOAb, TgAb, Tg	Women aged 18–45 years with a singleton pregnancy, residence in the city for more than 10 years	< 150	150-249	Yes	TSH, preterm, low birthweight, misacarriage	No	Yes
Yang	2018	Cohort	1427	26	2nd, 3rd	China	July to september 2015	Sufficient	Maternal age, education, income, and working hours	Singleton birth, no chronic diseases, no thyroid disease or use thyroid drugs	<150	150-249	Yes	Preterm, low birthweight, miscarriage, stillbirth, small for gestational age, maternal hypothyroidism, maternal subclinical hypothyroidism	No	Yes
Zhang	2018	Cohort	761	28	1st, 2nd, 3rd	China	2015 to 2017	Sufficient	Maternal age, maternal BMI, gestation duration, mode of delivery, parity, maternal TSH, maternal UIC, neonatal sex, neonatal weight and height, trimester when mother joined the study	Healthy pregnant women, with no history of thyroid disease or any other chronic diseases	< 150	150-249	Yes	Neonatal TSH	No	Yes
Zhou	2018	Cohort	454	30	1st, 2nd	Australia	2011 to 2015	Mild deficiency	Mother's age, education, employment status, number of adults and children living in the household, maternal BMI, smoking, gestational age, parity,breastfeeding at discharge from hospital after birth	Pregnant women with no history of thyroid disease, a fetal abnormality in the current pregnancy, drug or alcohol abuse	< 150	150-249	No	The cognitive, language, and motor composites of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)	No	No, descriptive analysis
Alvarez-Pedrerol	2009	Cohort	479	31	3rd	Spain	2004 to 2006	NR	Parity, mother's weight and age, gestational age, mother's smoking habits	Pregnant women without thyroid disorder, child born with some malformations, women whose children had been born before 34 weeks of gestation	<150	150–249	Yes	Small for gestational age	No	Yes
Amouzegar	2014	Cohort	362	25	1st	Iran	2004 to 2006	Sufficient	NR	Singleton pregnancies, women not taking iodine supplementation, without thyroid disease	<150	>150	Yes	TSH	No	Yes
Azizi	2011	Cross-sectional	202	25	1st, 2nd, 3rd	Iran	2005 to 2006	Sufficient	NR	Singleton pregnancy	<150	>150	Yes	Neonatal TSH (TSH on cord blood >13 mIU/l)	No	Yes
Bath	2013	Cohort	958	29	1st	England	1991 to 1992	Mild deficiency	Maternal age, stressful life-event scores, maternal education, alcohol intake, breastfeeding, crowding, ethnic origin of the child, family adversity during pregnancy, fish-oil supplements, sex, intake of iron estimated, mother's parenting score, parity, paternal education, smoking status, birthweight, maternal depression, and pre term birth	Singleton pregnancy, 17–44 years	<150	>150	No	IQ in the offspring at age 8 years and reading ability at age 9 years	Yes	No, descriptive analysis

Study	Year	Study Design	Pregnant women (n)	Mean Age (Years)	Gestational Trimester	Country	Period	Iodine Status	Confounders	Participants	Exposition (UIC µg/L)	Control (UIC µg/L)	Thyroid Antibody	Outcomes	Correc creat	Inclusion on meta-analyses
Charoenratana	2015	Cohort	390	28	1st, 2nd, 3rd	Thailand	2013 to 2014	NR	Parity, number of antenatal visits, gestational age at delivery, route of delivery, pregnancy outcomes, gestational diabetes, pre-eclampsia or pregnancy-induced hypertension, post-partum haemorrhage, low Apgar scores	Singleton pregnancy, no thyroid diseases, no receiving iodine-containing supplements	< 150	> 150	Yes	Preterm, Low birthweight, stillbirth	No	Yes
Cho	2015	Cross-sectional	119	33	1st, 2nd, 3rd	Korea	2012 to 2013	Sufficient	Age, weight, height, BMI, smoking, parity, region of residence, thyroid auto-antibodies	Singleton pregnancies, no history of thyroid disease or medication usage	<150	150–249	Yes	Maternal subclinical hypothyroidism	Yes	Yes
Delshad	2016	Cross-sectional	TSH: 800, MH/MSH: 1012	27	1st, 2nd, 3rd	Iran	2013 to 2014	Sufficient	Age, parity, gestational age	Health pregnant women, singleton pregnancy, aged 20–40 years, no smokers	TSH <100 MH/MSH<150	150–249	Yes	TSH, maternal subclinical hypothyroidism, maternal hypothyroidism	No	Yes
Ghassabian	2014	Cohort	1525	29	1st, 2nd	Netherland	2002 to 2006	Sufficient	Child's sex and age, maternal age and education, child's ethnic background, birth order, history of breastfeeding at age 6 months, paternal age, maternal BMI, maternal history of smoking, maternal IQ, marital status, paternal education, maternal psychopathology in pregnancy, maternal folate concentration in early pregnancy, household income, time of urine sampling in pregnancy	Singleton pregnancy	< 150	> 150	No	Non-verbal IQ and language comprehension scores from children at age 6 years and TSH	Yes	Yes
Habimana	2014	Cross-sectional	152	27	1st, 2nd, 3rd	Democratic Republic of Congo	2009 to 2011	Mild deficiency	Age, parity, socioeconomic area	Singleton pregnancy, with no thyroid disease	< 150	150-249	Yes	TSH, maternal subclinical hypothyroidism, maternal hypothyroidism	No	Yes
Hynes	2013	Cohort	226	29	2nd	Australia	1999 to 2001	Mild deficiency	Maternal age, gestational age at the time of UI collection, gestational length, birth weight, sex, parental education and occupation, indigenous status	Singleton pregnancy	< 150	>150	No	Preterm, low birthweight; education assessment at aged 9 years (NAPLAN: Spelling, Grammar, Reading, Writing, Numeracy score; SARIS: English-literacy score, Mathematics-numeracy score)	No	Yes
Mills	2019	Cohort	329	29	NR	USA	2005 to 2009	Sufficient	Woman's age, difference between female and male partner's age, woman's race/ethnicity, woman's educational level, household income, BMI, diabetes mellitus, periconceptional consumption of alcohol per day, periconceptional smoking per day, periconceptional consumption of caffeine per day, history of hypothyroid disease, history of hyperthyroid disease, creatinine	Pregnant women aged 18–40 years	< 150	>150	No	Pregnancy Loss	Yes	No, missing data
Medici	2013	Cohort	Neonatal TSH: 1067, Maternal subclinical hypothyrodism:1087	30	1st	Netherland	2002 to 2006	Sufficient	Maternal age, socioeconomic status, ethnicity, thyroid disease, thyroid (interfering) medication usage, first trimester vomiting	Singleton pregnancy	< 150	> 150	Yes	Neonatal TSH, maternal subclinical hypothyrodism	No	Yes
Moreno-Reyes	2013	Cross-sectional	1311	28	1st, 3rd	Belgium	2010 to 2011	Mild deficiency	Sociodemographic and socioeconomic characteristics, smoking and alcohol drinking behavior, thyroid diseases, use of iodine-containing supplements and food consumption, use of iodized household salt, BMI	Pregnant women	< 150	150 - 249	Yes	Maternal TSH (graphic)	Yes	No, missing data
Murcia	2011	Cohort	522	30	1st	Spain	2005 to 2007	Mild deficiency	Educational level, social class, cohabitant, employed at baby's age 1 year, smoking, history of thyroid disease, infant sex, breastfeeding, fetal growth restriction	Pregnant women	< 100	150-249	No	Children before 18 months evaluated for neuropsychological development (Mental Development Index, Psychomotor Development Index - Bayley Scales of Infant Development)	No	No, descriptive analysis
Oguz	2012	Cross-sectional	162	25	2nd	Turkey	October to december 2008	Sufficient	Socioeconomic level, household income, education duration, use of iodized salt	Pregnant women aged 16 - 41 years with no thyroid pathologies or any other acute or chronic diseases at the time of presentation and no use medicines that might affect thyroid hormone metabolism or iodine bioavailability	<150	>150	No	Goiter prevalence ascertained by clinical neck examination	No	No, different instrument analysis
Olivares	2012	Cohort	77	25	NR	Argentine	March to august 2009	Mild to moderate deficiency	Arterial hypertension, diabetes, smoking, maternal BMI, smoking	Pregnant women	<150	>150	No	Low birthweight	No	Yes
Rajatanavin	2007	Cross-sectional	203	NR	NR	Thailand	2002 to 2003	Mild deficiency	NR	Pregnant women	<150	>150	No	Neonatal TSH	No	No, missing data
Rebagliato	2013	Cohort	1519	NR	1st, 3rd	Spain	2003 to 2008	Mild deficiency	Maternal age, sex, history of thyroid disease, maternal origin, mixed social class, breastfeeding, parity, educational level, employment at 1 year of age	Pregnant women	<150	150-249	No	Cognitive and psychomotor development of infants was evaluated using the Bayley Scales of Infant Development	No	No, descriptive analysis
Rebagliato	2010	Cross-sectional	1168	31	1st, 2nd	Spain	2004 to 2008	Mild deficiency	Iodine-intake, maternal age, country of origin, educational level, pre-pregnancy BMI, parity, gestational age	Pregnant women	<150	150-249	No	Maternal Subclinical Hypothyrodism	No	Yes
Ruiz	2009	Cross-sectional	154	33	1st	Spain	2006 to 2007	Mild deficiency	NR	Pregnant women aged > 18 years with no thyroid pathologies or use medicines that might affect thyroid hormone metabolism	<150	>150	No	TSH	No	Yes
Rydbeck	2014	Cohort	808	26	1st	Bangladesh	2002 to 2003	Sufficient	Maternal BMI, parity, level of formal education, season of birth, gestational age at birth, newborn sex, food and micronutrient supplementation, maternal urinary cadmium and arsenic metabolites	Pregnant women, viable fetus, no severe maternal illnesses	<100	>100	No	Low birth weight, birth lenght	No	Yes
Shi	2015	Cross-sectional	TSH: 3950 Maternal Hypothyrodism/Maternal Subclinical Hypothyrodism: 5921	NR	1st	China	2012 to 2014	Sufficient	Age, weeks of gestation, BMI, TPOAb, TgAb	Pregnant women aged 19 – 40 years, singleton pregnancy, no smokers, no history of thyroid disease or any other chronic diseases, subjects on any medical regimen before pregnancy that may affect thyroid function, such as glucocorticoids, dopamine, or antiepileptic drugs	<150	150-249	Yes	TSH, maternal hypothyroidism, maternal subclinical hypothyroidism	No	Yes
Soldin	2005	Cross-sectional	152	NR	1st, 2nd, 3rd	USA	1988 to 1994	Sufficient	NR	Pregnant women with no thyroid disease, goiter, or use of thyroid medications	50 -100	>200	No	TSH	Yes	Yes
Vila	2008	Cohort	35	29	1st, 3rd	Spain	1st semester of 2000	Mild deficiency	Iodine supplements, active smokers	Pregnant women	< 150	>150	No	Thyroid volume calculated by thyroid US	No	Yes
Yoganathan	2015	Cohort	420	29	3rd	Sri Lanka	NR	NR	Average intake of iodine rich food by the mothers, age, height, weight, educational attainment	Pregnant women	<150	150-249	No	Preterm	No	Yes

Study	Year	Study Design	Pregnant women (n)	Mean Age (Years)	Gestational Trimester	Country	Period	Iodine Status	Confounders	Participants	Exposition (UIC µg/L)	Control (UIC µg/L)	Thyroid Antibody	Outcomes	Correc creat	Inclusion on meta-analyses
Zhang	2021	Cohort	596	30	1st	China	2017 to 2019	Sufficient	Age, BMI, birth order, history of spontaneous abortion	Singleton pregnancy, with no history of tumors, autoimmune diseases, heart disease, liver disease, kidney disease or chronic hypertension, as well as medications that may afect thyroid function	<150	150-249	Yes	TSH, maternal subclinical hypothyroidism, small for gestational age, miscarriage, low birthweight, preterm, birth lenght	Yes	Yes
Gargari	2020	Cohort	884	29	3rd	Iran	2017 to 2018	Sufficient	Age, gestational age, weight gain during pregnancy, mother educational status, smoking, parity, time interval between the recent pregnancy, type of pregnancy, use of dietary complements during pregnancy	Pregnant women	<150	>150	No	Preterm	No	Yes
Saraiva	2018	Cross-sectional	233	26	1st	Brazil	2014 to 2017	Sufficient	Age greater than 30 years, moderate to severe obesity (BMI ≥ 35 kg/m2), multiparity, SCH, abnormal iodine concentration in table salt, thyroiditis, and smoking habitus	Pregnant women, singleton pregnancy, aged 18 to 35 years, with no history of chronic diseases or other diseases diagnosed, no use of levothyroxine, anti-thyroid drug or supplements containing iodine	< 150	150-249	Yes	Maternal subclinical hypothyroidism, TSH, thyroid volume	No	Yes
Corcino	2019	Cohort	243	26	1st, 3rd	Brazil	2014 to 2017	Sufficient	Age, iodine concentration in table salt, gestational age, BMI at study entry, TSH at the time of urine collection, smoking habits, multiparity (≥3 labours) and positivity for serum thyroid antibodies	Pregnant women, singleton pregnancy, aged 18 to 35 years, with no history of chronic diseases or other diseases diagnosed, no use of levothyroxine, anti-thyroid drug or supplements containing iodine	<150	>150	Yes	TSH	No	No, same population of Saraiva and Morais studies
Morais	2020	Cohort	131	27	1st, 3rd	Brazil	2014 to 2017	Sufficient	Iodine status, maternal age, BMI, smoke habit, parity, diagnosis of SCH, positive TPOAb, use of LT4 or iodine-containing multivitamins during pregnancy	Pregnant women, singleton pregnancy, aged 18 to 35 years, with no history of chronic diseases or other diseases diagnosed, no use of levothyroxine, anti-thyroid drug or supplements containing iodine	<150	150-249	Yes	Preterm, low birthweight, miscarriage, stillbirth, small for gestational age, maternal subclinical hypothyroidism	No	Yes
Schiller	2020	Cross-sectional	100	32	1st	Israel	NR	Mild deficiency	Age, gestational age, school education, BMI, parity, smoker,positive family history of thyroid disease, iodine containing supplements consumption	Singleton pregnancy, with no previous thyroid disease	< 150	>150	Yes	TSH	No	Yes
Yang	2020	Cross-sectional	1243	NR	1st, 2nd, 3rd	China	2015	Sufficient	TPOAb, TgAb	Pregnant women	< 150	150-249	Yes	TSH, maternal hypothyroidism, maternal subclinical hypothyroidism, birth lenght	No	Yes
Guo W	2020	Cross-sectional	274	29	1st	China	2016 to 2017	Sufficient	TPOAb, TgAb	Pregnant women, singleton pregnancy, aged 18 to 35 years, with no history of chronic diseases or personal/family history of thyroid disease or auto- immune diseases; and not taking iodine supplements during pregnancy	<100	150-249	Yes	TSH, thyroid volume	No	Yes
Guo M	2020	Cross-sectional	500	NR	1st, 2nd, 3rd	China	2017 to 2019	Sufficient	TPOAb	No thyroid function or structural abnormalities or auto-immune disease, hypertension, diabetes, and on treatment for thyroid disease	< 150	>150	Yes	Maternal hypothyroidism, maternal subclinical hypothyroidism	No	Yes
Kampouri	2022	Cohort	1052	26	1st	Bangladesh	2002 to 2003	Deficient	Age, height, weight, delivery date, education, parity, family socioeconomic status index	Pregnant women, singleton pregnancy	< 150	> 150	No	Cognitive abilities at 5 and 10 years of age	No	No, descriptive analysis
Cui	2021	Cohort	6128	29	1st, 2nd, 3rd	China	2016 to 2018	Sufficient	Mother's age and education	Pregnant women	< 150	150-249	No	Preterm, low birthweight, congenital malformations	No	Yes
Wang	2022	Cross-sectional	1116	28	1st	China	January to December 2019	Sufficient	TPOAb, TgAb	Pregnant women, aged 19–43 years, with no history of thyroid diseases or chronic diseases, not taken an iodine-containing multivitamin or iodinated contrast agents before pregnancy	< 150	150-249	Yes	TSH, maternal hypothyroidism, maternal subclinical hypothyroidism	No	Yes

Abbreviations: UCI (urinary iodine concentration); NR (not related); BMI (body mass index); TPO Ab (thyroid peroxidase antibodies); FT4 (free thyroxine); Tg (thyroglobulin); TgAb (antithyroglobulin antibody); TSH (thyroid stimulating hormone); IQ (intelligence quotient); SCH (subclinical hypothyroidism), hCG (chorionic gonadotropin)

Risk of Bias

The risk of bias assessment was performed using risk of bias tools for etiology and risk studies standardized by the JBI. We used specific tools for cohort (Figure 2A) and cross-sectional (Figure 2B) studies.

		Critical appraisal checklist for cohort studies											
AUTHOR	**YEAR**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Include?**
Berg	2017	Y	Y	Y	Y	N	Y	Y	Y	Y	NA	Y	Y
Chen	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Hynes	2017	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Kianpour	2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Levie	2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Markhus	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Murcia	2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Nazarpour	2019	Y	Y	Y	N	NA	Y	Y	Y	Y	NA	Y	Y
Ruiz Ochoa	2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Torlinska	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Xiao	2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Yang	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Zhang	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Zhou	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Alvarez-Pedrerol	2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Amouzegar	2014	Y	Y	Y	N	NA	Y	Y	Y	Y	NA	Y	Y
Bath	2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Charoenratana	2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Corcino	2019	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y
Ghassabian	2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Hynes	2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Mills	2019	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Medici	2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Murcia	2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Olivares	2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Rebagliato	2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Rydbeck	2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Vila	2008	Y	Y	Y	Y	N	Y	Y	Y	Y	NA	Y	Y
Yoganathan	2015	Y	Y	Y	N	NA	Y	Y	Y	Y	NA	Y	Y
Zhang	2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Morais	2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Kampouri	2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Cui	2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y

Figure 2A. Risk of bias assessment for cohort studies

		Critical appraisal checklist for analytical cross-sectional studies								
AUTHOR	**YEAR**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Include?**
Abel	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gyamfi	2018	Y	Y	Y	Y	Y	N	Y	Y	Y
Koyuncu	2018	Y	Y	Y	Y	N	N	Y	Y	Y
Mioto	2018	Y	Y	Y	Y	N	N	Y	Y	Y
Pan	2019	Y	Y	Y	Y	Y	N	Y	Y	Y
Saraiva	2018	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ulu	2017	Y	Y	Y	Y	Y	N	Y	Y	Y
Azizi	2011	Y	Y	Y	Y	N	N	Y	Y	Y
Delshad	2016	Y	Y	Y	Y	Y	N	Y	Y	Y
Habimana	2014	Y	Y	Y	Y	Y	N	Y	Y	Y
Moreno-Reyes	2013	Y	Y	Y	Y	Y	N	Y	Y	Y
Oguz	2012	Y	Y	Y	Y	Y	N	Y	Y	Y
Rajatanavin	2007	Y	Y	Y	Y	N	N	Y	Y	Y
Rebagliato	2010	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ruiz	2009	Y	Y	Y	Y	N	N	Y	Y	Y
Shi	2015	Y	Y	Y	Y	Y	Y	Y	Y	Y
Soldin	2005	Y	Y	Y	Y	N	N	Y	Y	Y
Cho	2015	Y	Y	Y	Y	Y	N	Y	Y	Y
Gargari	2020	Y	Y	Y	Y	Y	Y	Y	Y	Y
Schiller	2020	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yang	2020	Y	Y	Y	Y	Y	Y	Y	Y	Y
Guo W	2020	Y	Y	Y	Y	Y	Y	Y	Y	Y
Guo M	2020	Y	Y	Y	Y	N	N	Y	Y	Y
Wang	2022	Y	Y	Y	Y	Y	N	Y	Y	Y

Figure 2B. Risk of bias assessment for cross-sectional studies

Meta-analysis

Data from 41 studies were plotted in the meta-analyses. Details of each outcome are described below.

Maternal Outcomes

Regarding maternal outcomes: six studies evaluated spontaneous miscarriage[15,17,23,29,34,35], seven analyzed maternal hypothyroidism[1,35,43,44,63,64,68], 13 studies evaluated maternal subclinical hypothyroidism[1,15,17,35,42–44,46,52,58,63,64,68], four analyzed thyroid volume [27,56,58,65], 21 evaluated maternal TSH measurement[1,14,17–19,24,27,29–31,34,39,43,44,53,55,58,62,63,65,68].

For miscarriage, we found no difference between exposure and control groups [RR: 0.87, IC 95% 0.64 to 1.18, six studies, 4841 participants, I^2=0, figure 3; low certainty of evidence (table 2)].

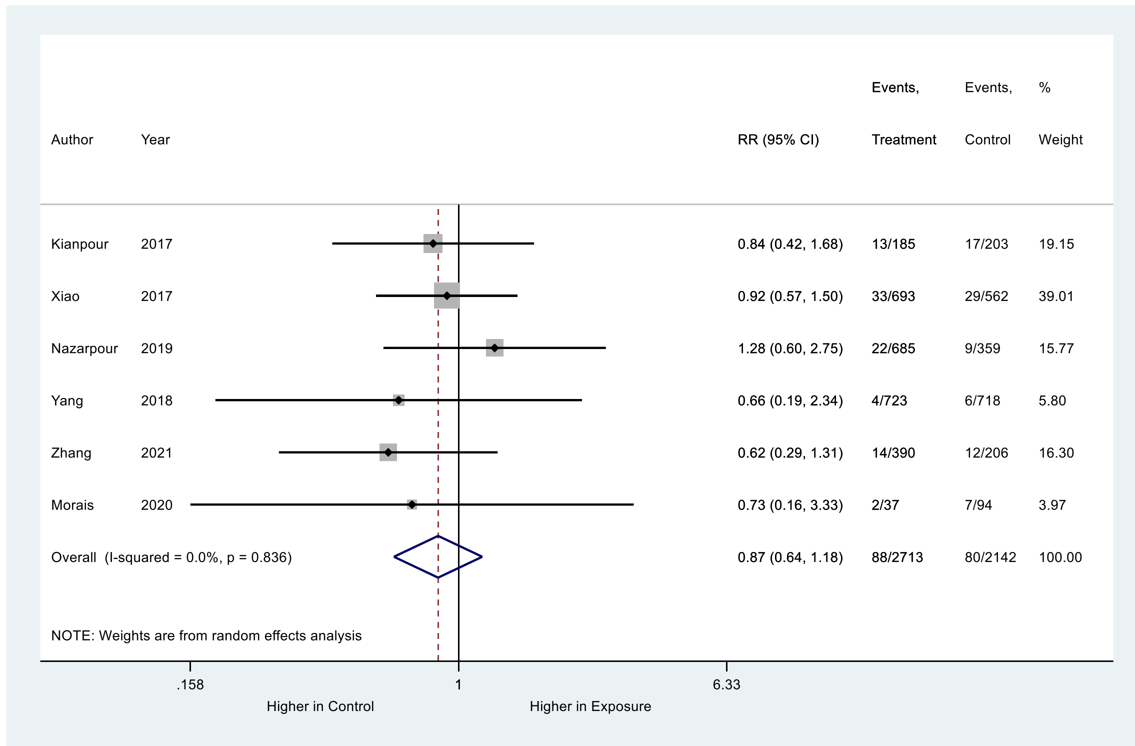

Figure 3. Miscarriage meta-analysis

Table 2. Summary of findings - Quality of evidence according to GRADE approach of association between UIC in pregnancy with maternal and newborn outcomes

Outcomes	Anticipated absolute effects * (95% CI)	
	Risk with [comparison]	Risk with [exposure]
Preterm Birth	58 per 1.000	**69 per 1.000** (55 to 86)
Low Birthweight	65 per 1.000	**70 per 1.000** (56 to 89)
Stillbirth	8 per 1.000	**5 per 1.000** (2 to 13)
Miscarriage	37 per 1.000	**32 per 1.000** (24 to 44)
Maternal Subclinical Hypothyroidism	37 per 1.000	**39 per 1.000** (32 to 47)
Maternal TSH measurement	The mean TSH measurement was 0	MD **0.01** UI/mL lower (0.06 lower to 0.05 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD**: mean difference; **OR**: odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Uper limit of confidence interval over 1.25
b. Low limit of confidence interval under 0.75

Concerning maternal hypothyroidism, we found no difference between the exposure and control groups (RR: 1.19, IC 95% 0.84 to 1.69, seven studies, 11371 participants, I^2=0, figure 4).

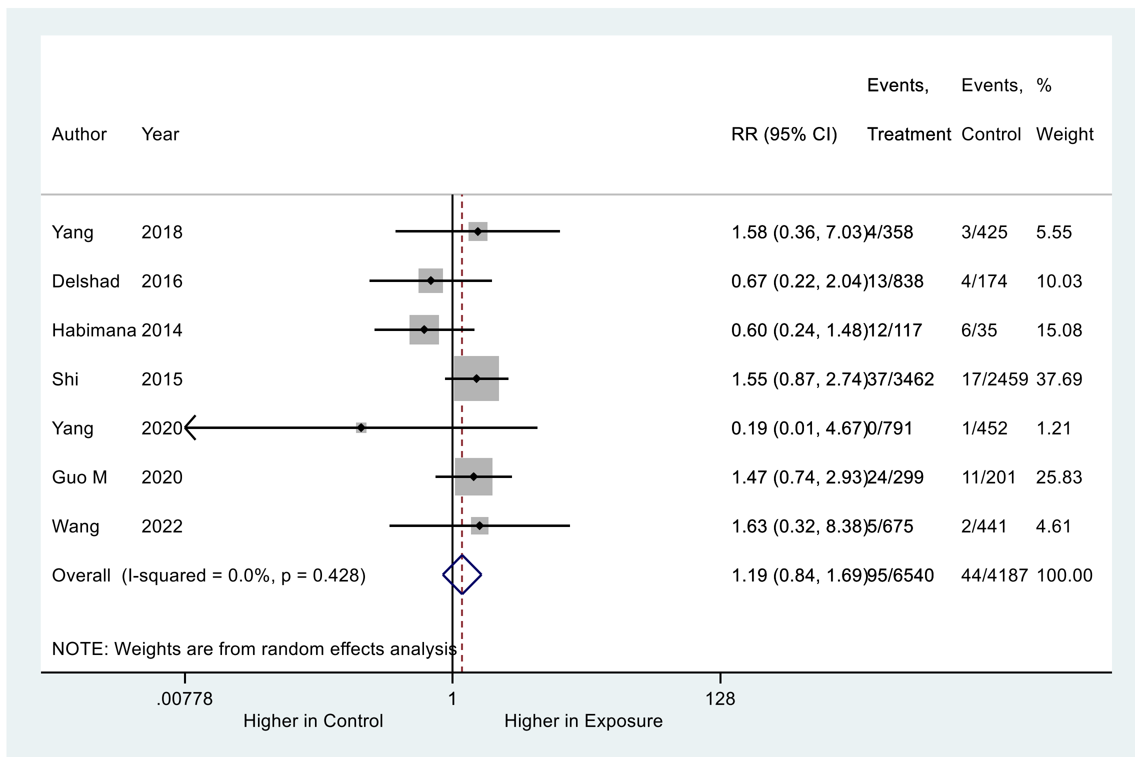

Figure 4. Maternal hypothyroidism meta-analysis

To maternal subclinical hypothyroidism, we found no difference between the exposure and control groups [RR: 1.05, IC 95% 0.87 to 1.26, 13 studies, 14705 participants, I^2=7.7%, figure 5; low certainty of evidence (table 2)].

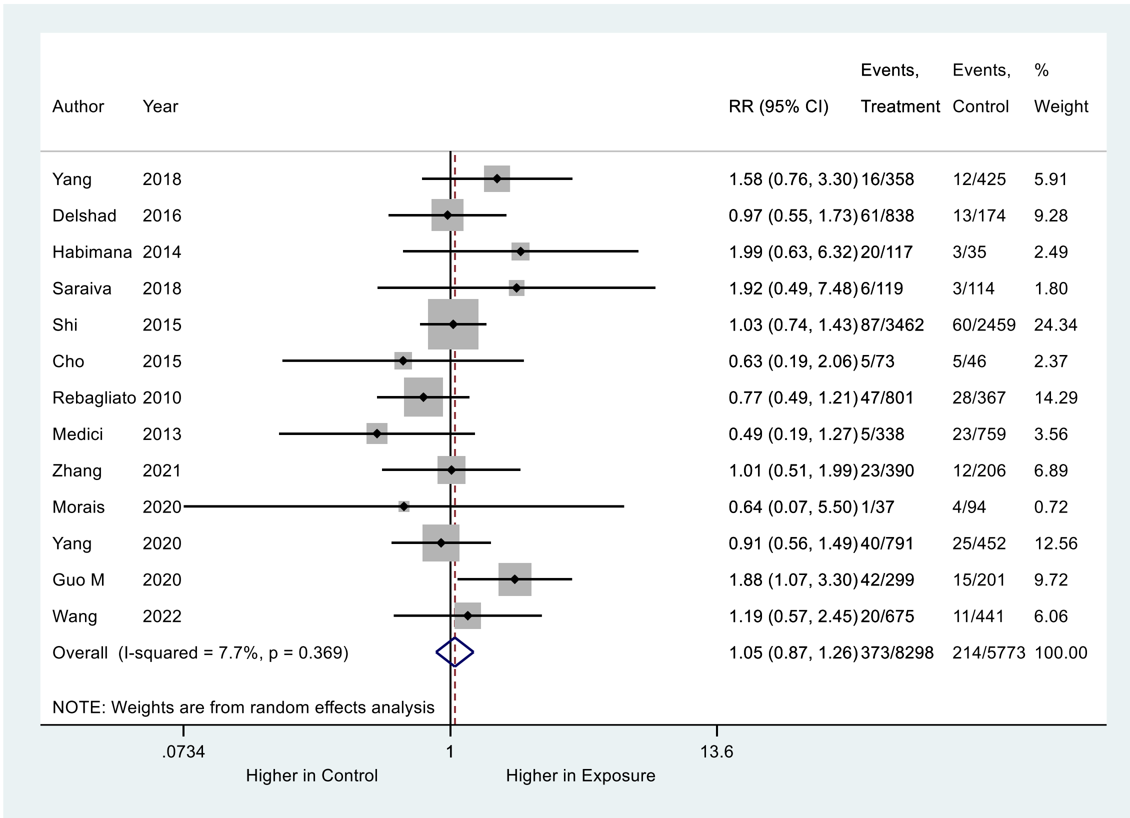

Figure 5. Maternal subclinical hypothyroidism meta-analysis

For thyroid volume, we found no difference between the exposure and control groups (RR: -0.50, IC 95% -1.02 to 0.02, four studies, 620 participants, I^2=0, figure 6).

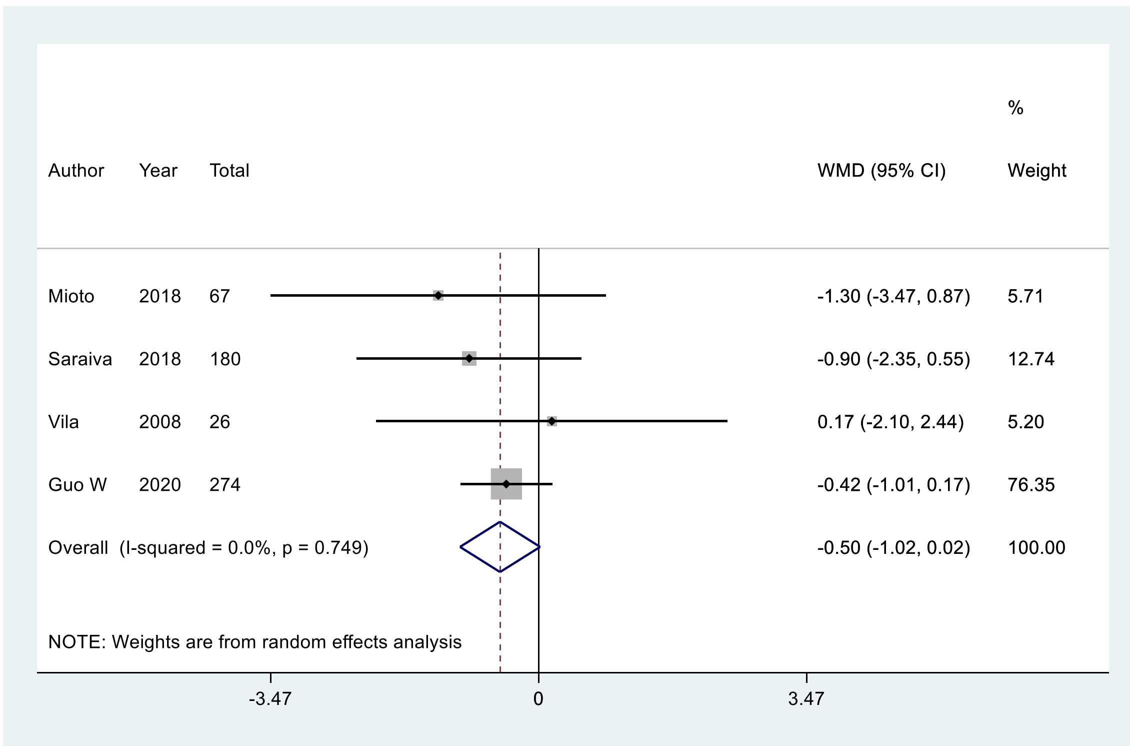

Figure 6. Thyroid volume meta-analysis

In relation to maternal TSH measurement, we found no difference between the exposure and control groups [RR: -0.01, IC 95% -0.06 to 0.05, 21 studies, 15438 participants, I^2=51.2%, figure 7; low certainty of evidence (table 2)]. In addition, no difference was seen, on TSH measurement, when we separated the groups, according to imputation or to UIC values used as control (figures 7A and 7B).

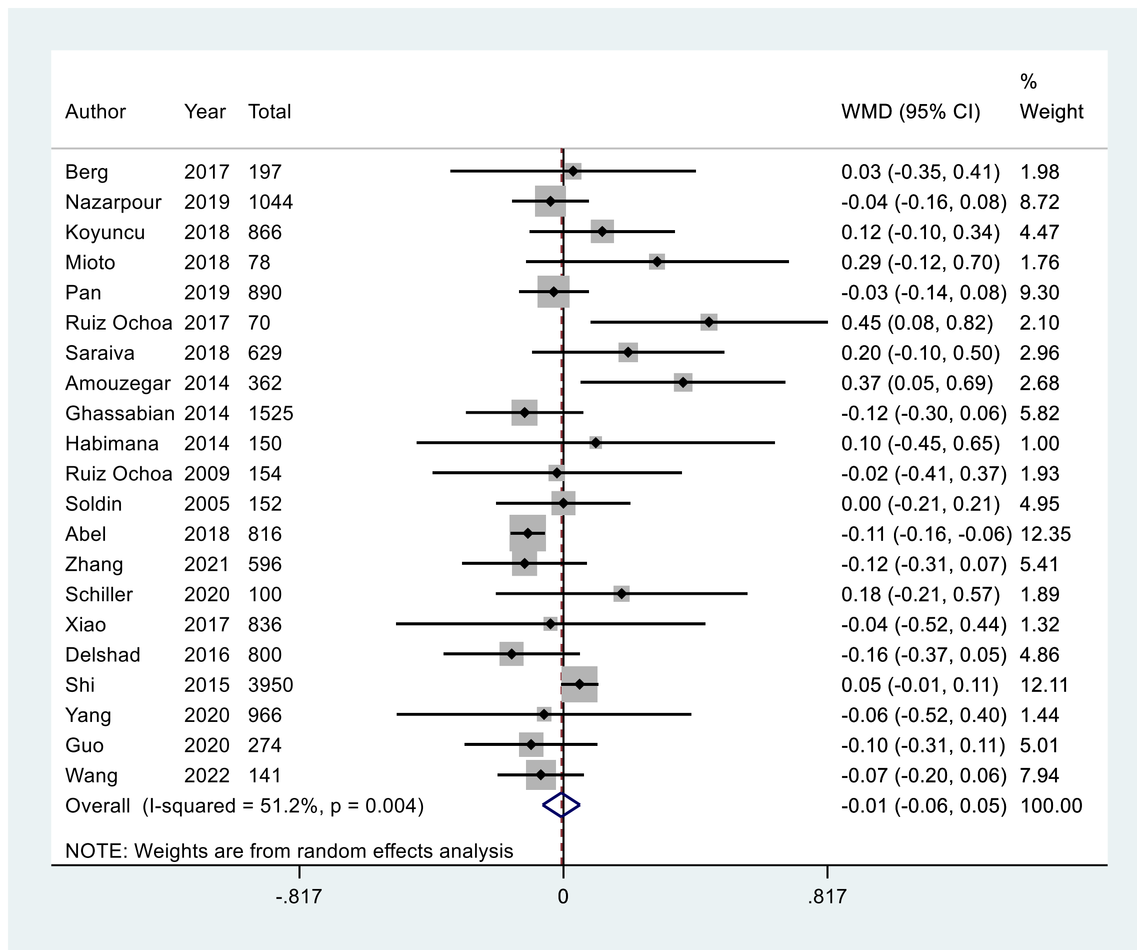

Figure 7. Maternal TSH measurement meta-analysis

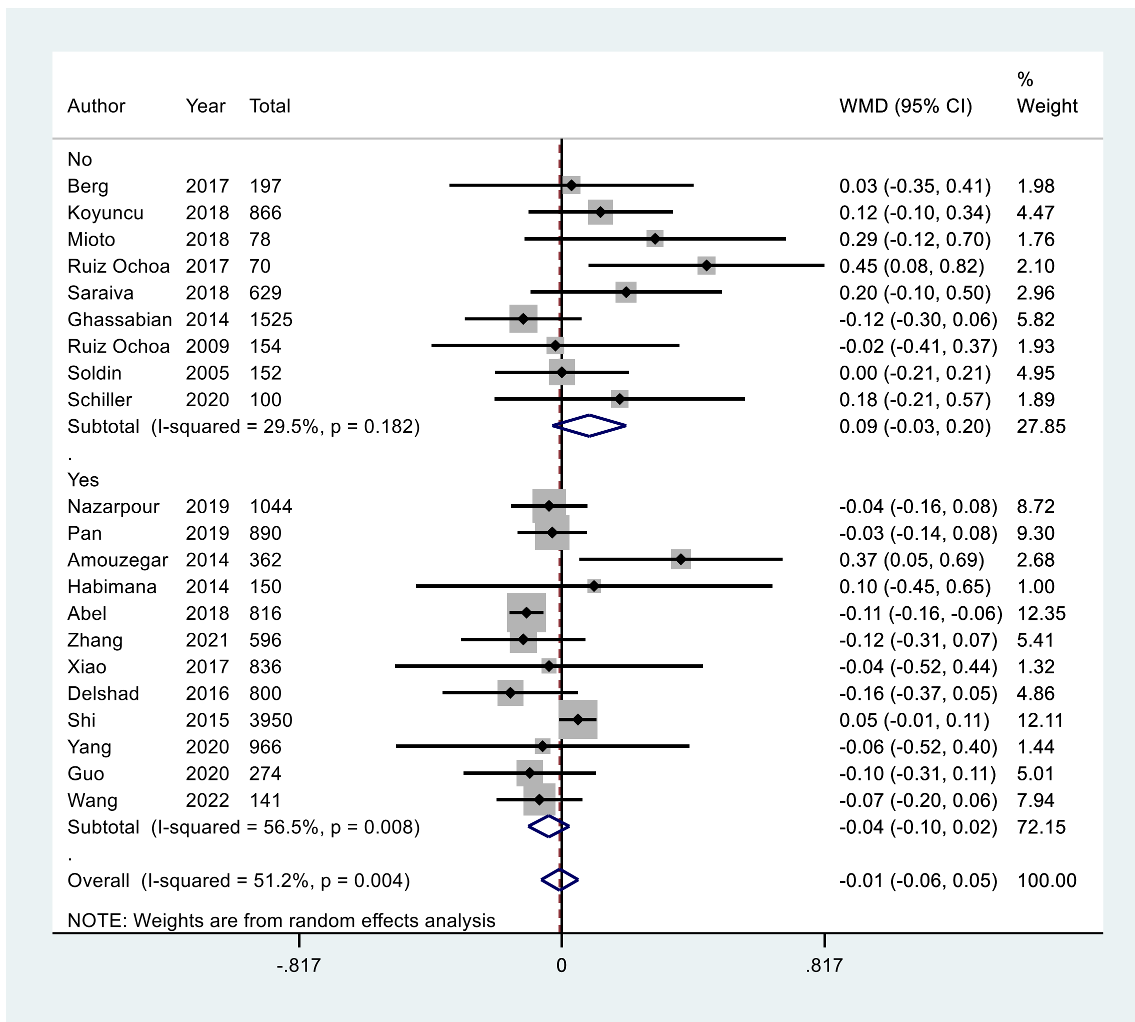

Figure 7A. Maternal TSH measurement meta-analysis, according to imputation

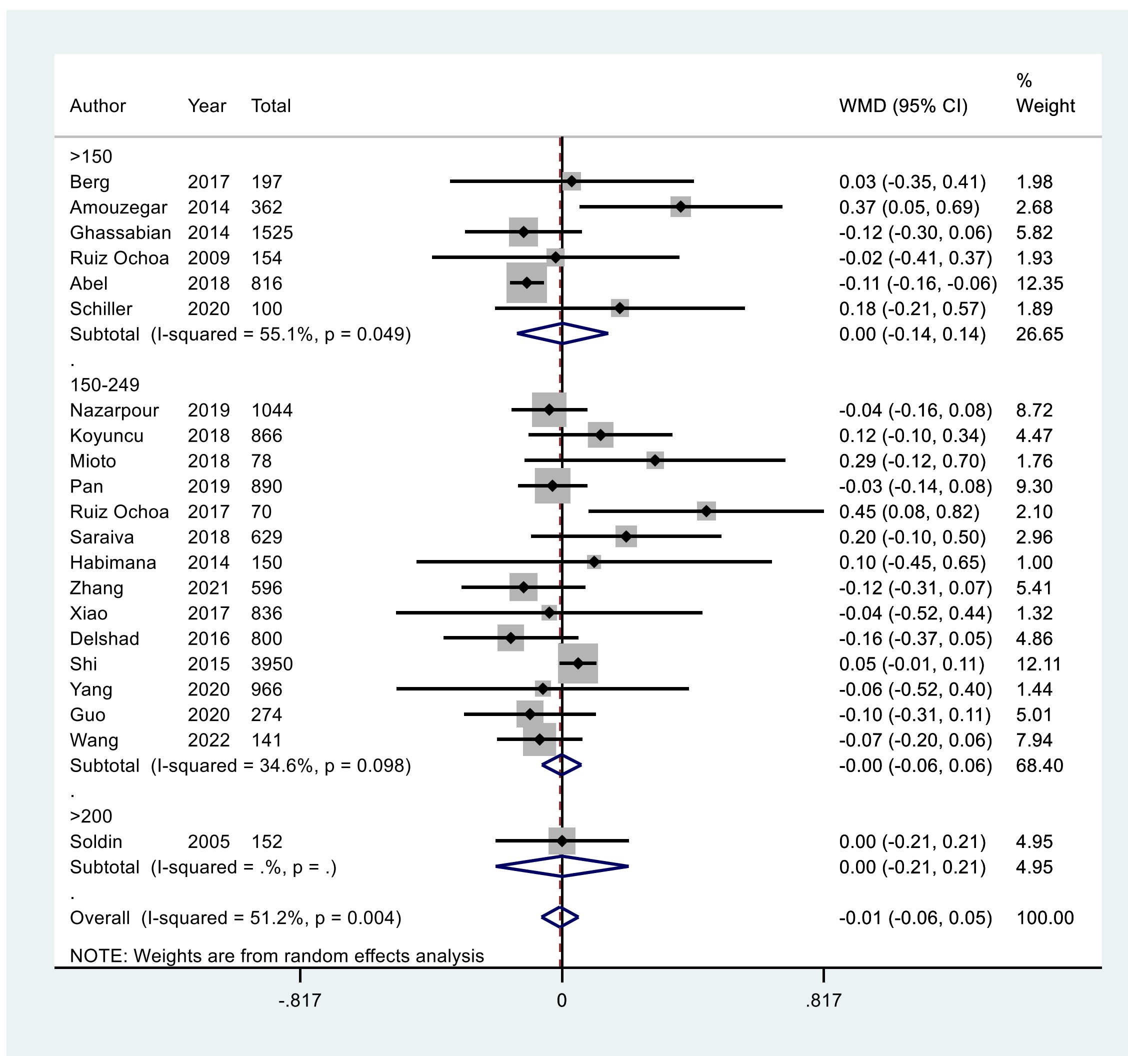

Figure 7B. Maternal TSH measurement meta-analysis, according to UIC values used as control

Neonatal outcomes:

Concerning neonatal outcomes, 11 studies evaluated preterm birth[15–17,29,32,34,35,41,45,57,66], four evaluated perinatal mortality (including stillbirth/fetal death and neonatal death)[15,29,35,41], nine studies analyzed low birthweight[15,17,34,35,41,45,50,54,66], five evaluated small for gestational age[15,17,32,35,38], birth length were performed by five studies[15,17,20,29,54] and three studies analyzed neonatal hypothyroidism or elevated TSH[36,46,61].

Regarding preterm birth, we found no difference between exposure and control groups [RR: 1.18, IC 95% 0.94 a 1.47, 11 studies, 15098 participants, I^2=44.8%, figure 8; very low certainty of evidence (table 2)]. Besides, no difference was seen, on preterm birth, when we separated the groups, according to UIC values used as control (figures 8A),

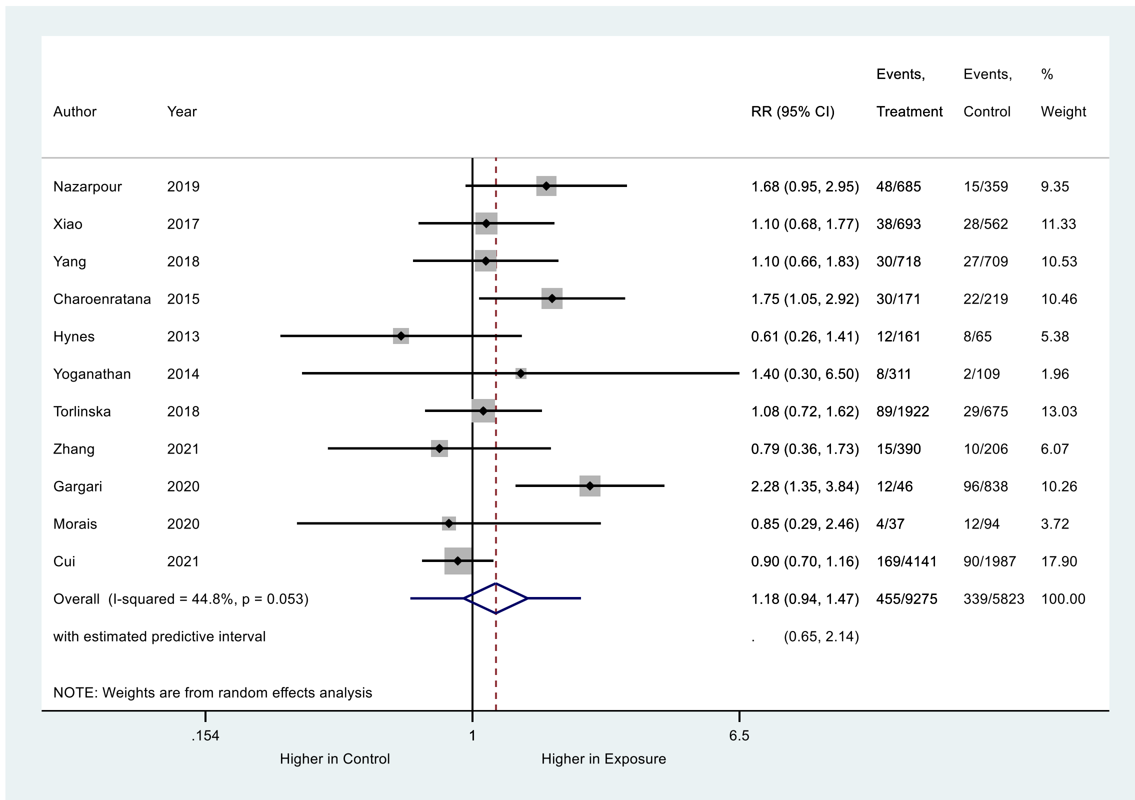

Figure 8. Preterm birth meta-analysis

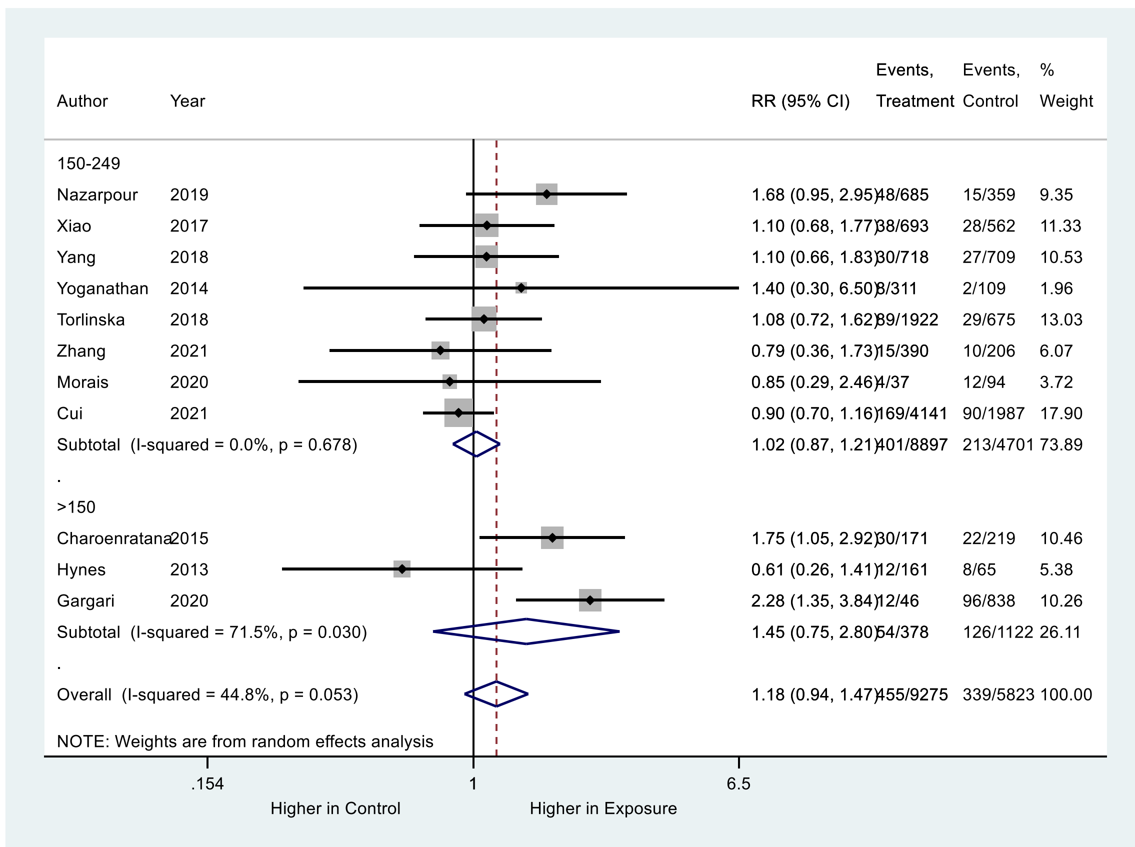

Figure 8A. Preterm birth meta-analysis, according to UIC values used as control

We found no difference between exposure and control groups in stillbirth (RR: 0.63, IC 95% 0.24 to 1.69, four studies, 2992 participants, I^2=13%, figure 9; very low certainty of evidence (table 2)].

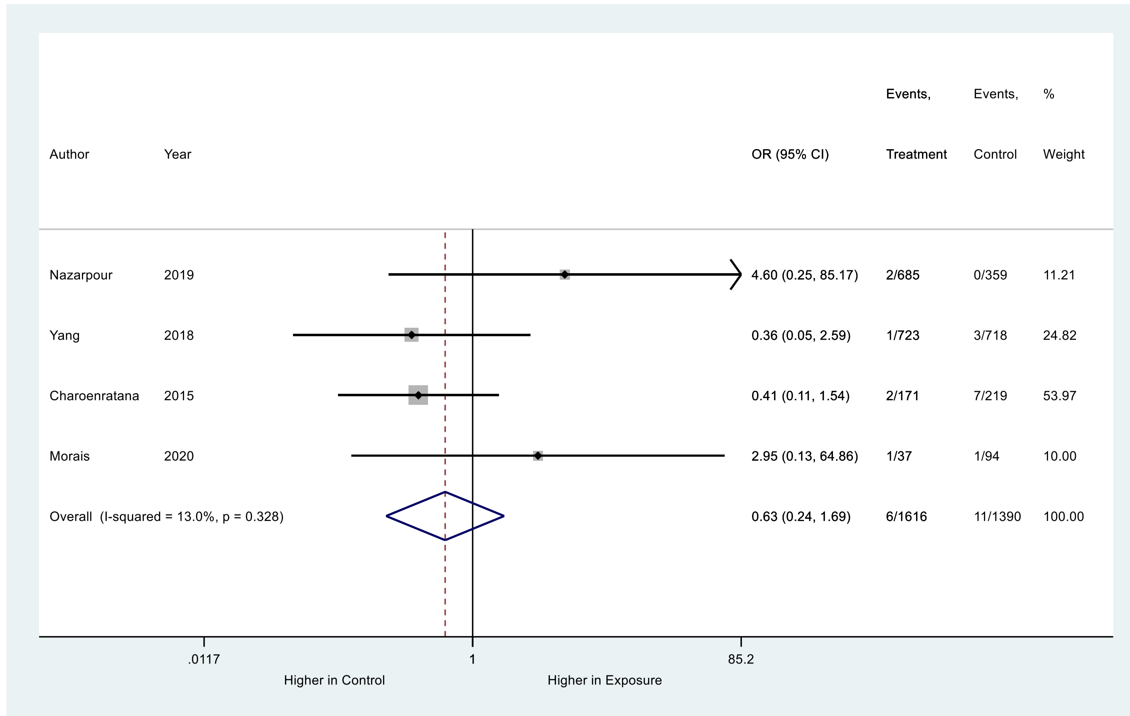

Figure 9. Stillbirth meta-analysis

Respecting low birthweight, we found no difference between the exposure and control groups [RR: 1.08, IC 95% 0.86 to 1.36, nine studies, 11038 participants, I^2=37.2%, figure 10; very low certainty of evidence (table 2)]. Besides, no difference was seen, on low birthweight, when we separated the groups, according to UIC values used as control (figures 10A),

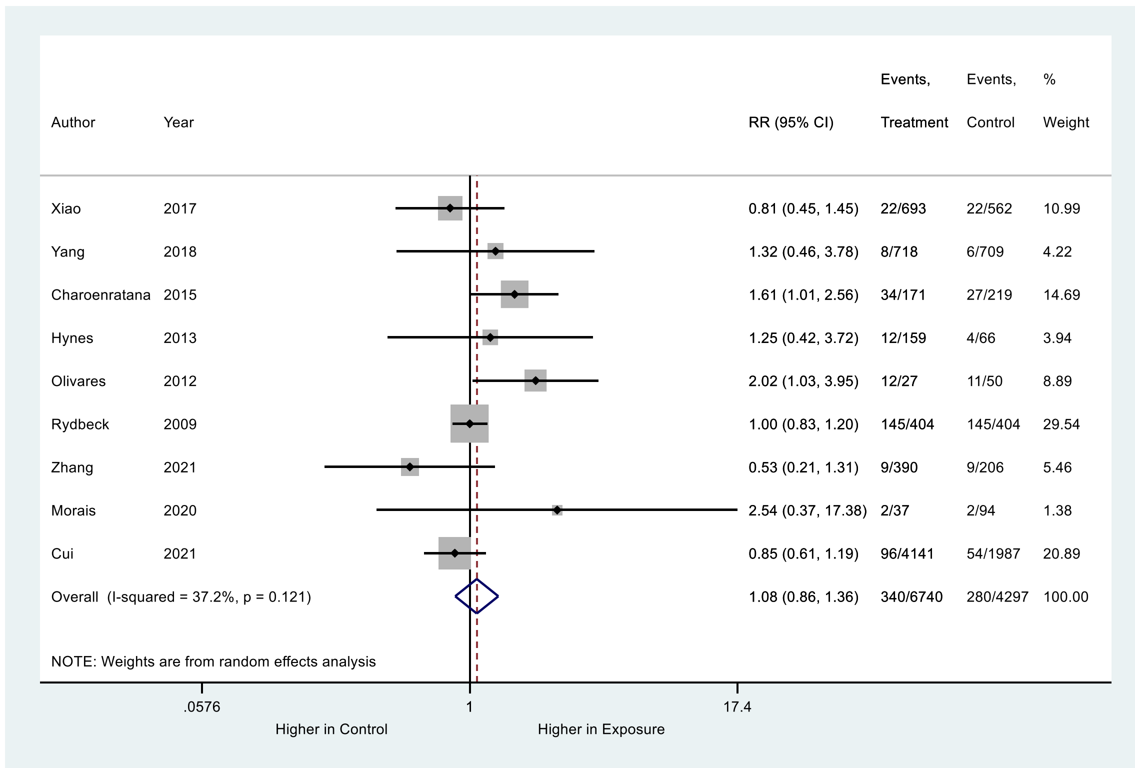

Figure 10. Low birthweight meta-analysis

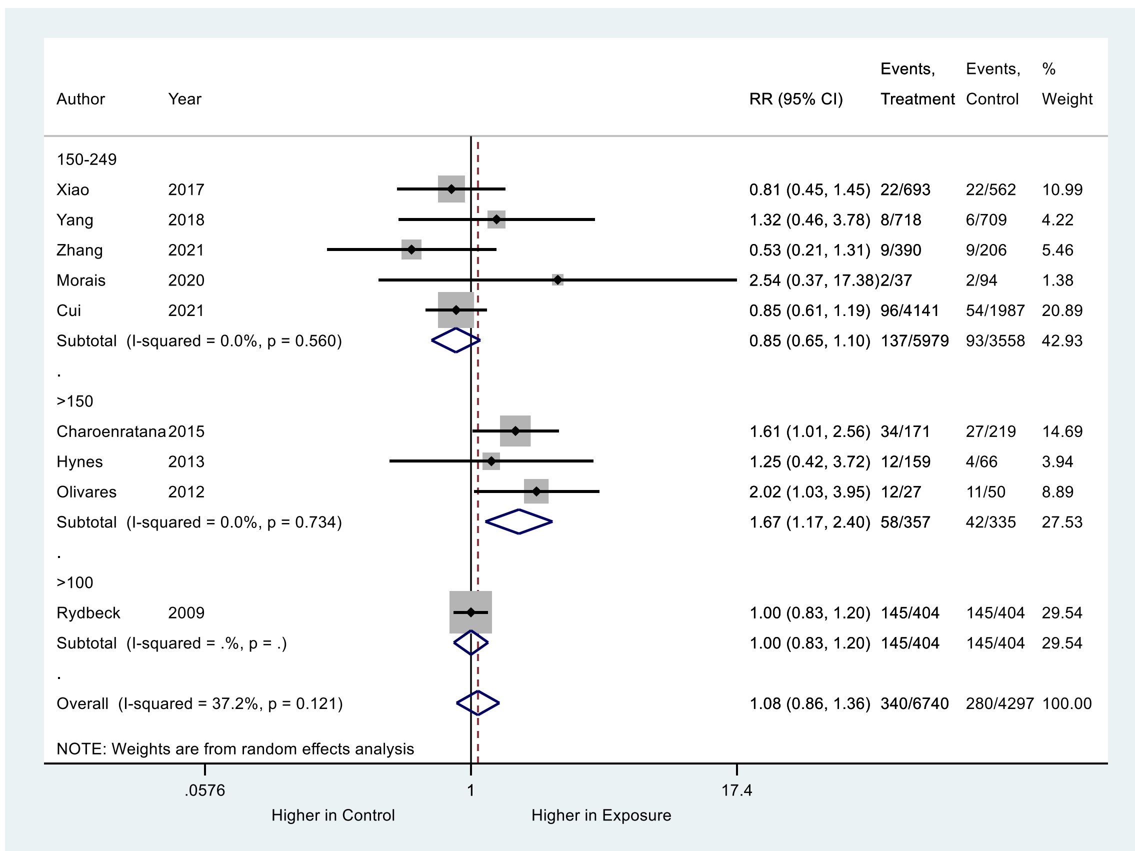

Figure 10A. Low birthweight meta-analysis, according to UIC values used as control

In relation to small for gestational age, we found no difference between exposure and control groups (RR: 1.11, IC 95% 0.90 to 1.37, five studies, 5230 participants, I^2=0, figure 11).

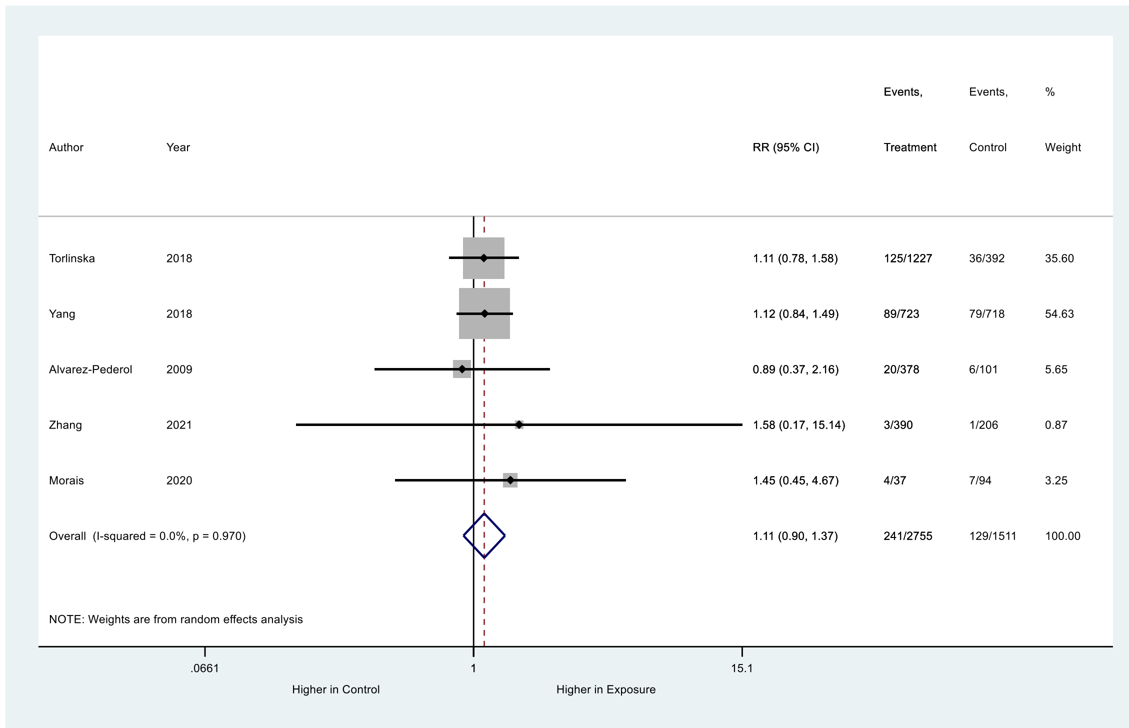

Figure 11. Small for gestational age meta-analysis

To birth length, we found no difference between exposure and control groups (RR: 0.13, IC 95% -0.12 to 0.37, five studies, 4831 participants, I^2=64.4%, figure 12).

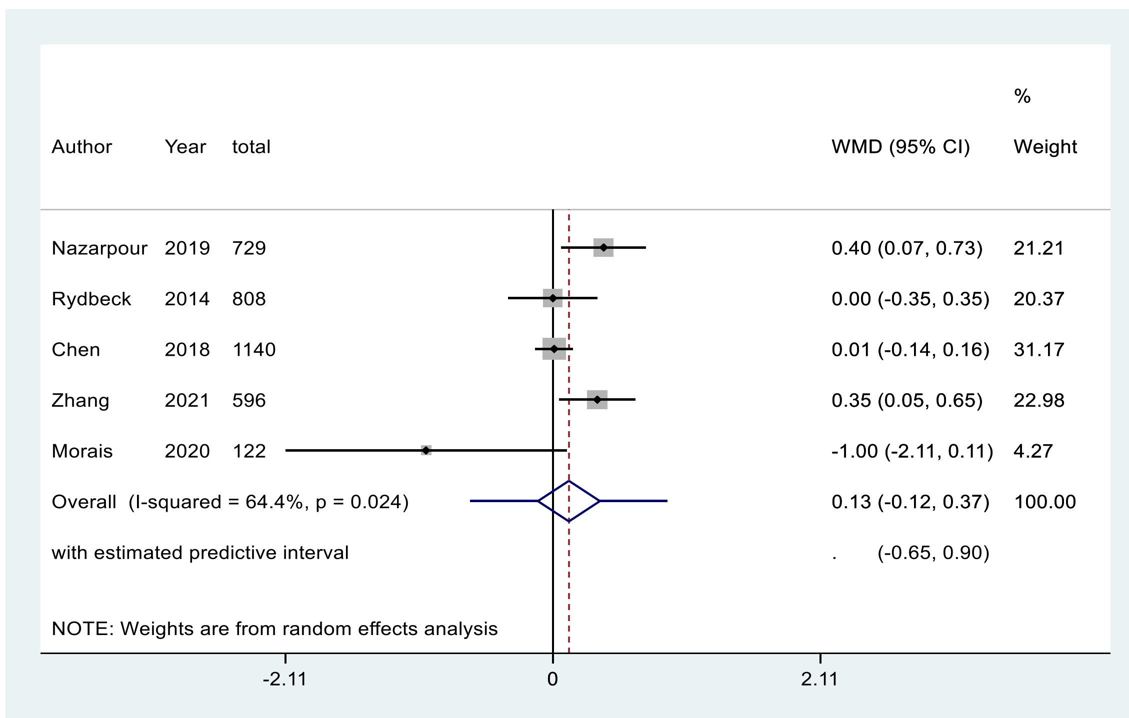

Figure 12. Birth length meta-analysis

Regarding elevated neonatal TSH, we found no difference between the exposure and control groups (RR: 1.29, IC 95% 0.77 to 2.18, three studies, 2233 participants, I^2=52.2%, figure 13).

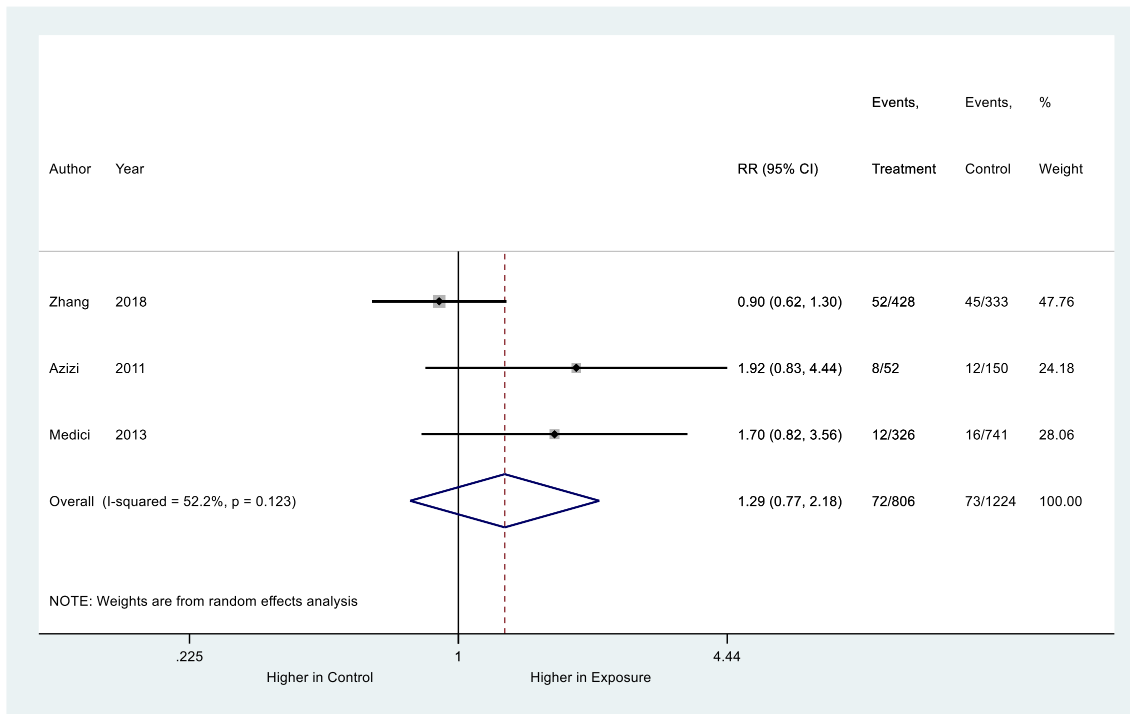

Figure 13. Elevated neonatal TSH meta-analysis

The following outcomes could not be plotted in a meta-analysis because no study has evaluated them: neonatal goiter, neonatal thyroid volume, infant death (death in the first year of life). The congenital malformations outcome was only assessed by a single study and no differences were found between the UIC groups[66].

Regarding the association between UIC < 150 µg/L and neuromotor development and IQ scores, it was not possible to perform a meta-analysis of these studies because they implemented different types of tests due to the different domains assessed and distinctive associations were recorded for non-matching ages. Therefore, a descriptive synthesis of these data was performed.

The results of the studies differ from each other, a variation was described on neuromotor development and IQ scores by some studies, however, not by others. Bath et al.[40] evaluated the association between maternal iodine status and child IQ at age 8 years and reading ability at age 9 years. They observed that children of women with an iodine-to-creatinine ratio < 150 µg/g were more likely to have scores in the lowest quartile for verbal IQ at 8 years old (OR 1.58, 95% CI 1.09 – 2.30, n=880; p=0.02), like for reading accuracy (OR 1.69, CI 1.15–2.49, n=839; p=0.007) and for reading comprehension (OR 1.54, CI 1.06–2.23, n=839; p=0.02) at 9 years old than those of mothers

with ratios of 150 µg/g or more. In 2017, Murcia et al.[28] assessed children using the McCarthy Scales of Children's Abilities up to 4–5 years old and also found an association between low UIC and lower cognitive scores in childhood when corrected for creatinine. After adjusting for creatinine, children of women with UIC/Cr <100 µg/L had 3.93 (CI −6.18 to –1.69) general cognitive scores lower than the reference (150–249 µg/L). Kampouri et al.[67] analyzed cognitive abilities assessed by the Wechsler Preschool and Primary Scale of Intelligence and Wechsler Intelligence Scale for Children from children at 5 and 10 years of age. In this study, maternal UIC < 150 µg/L was associated with lower full-scale scores at 5 and 10 years, especially verbal scales, when compared with the reference groups. Rebagliato et al.[51] assessed neuropsychological development using the Bayley Scales of Infant Development infants with median age of 16 months. In combined adjusted analyses, the study observed that infants from mothers with UICs in the range of 150–249 µg/L had a 2.3 point (CI −0.2, 4.9) increased in the mental scale score compared with those whose mothers had a UIC < 100 µg/L, although this association did not reach statistical significance. As well, Markhus et al.[26] explored the association between maternal UIC and child neurodevelopment at 6, 12 and 18 months of age using Bayley Scales of Infant and Toddler Development. UIC < 100 µg/L was associated with reduced receptive (p=0.025) and expressive language skills (p=0.002), but not with reduced cognitive or fine and gross motor skills. Likewise, Hynes et al.[45] compared educational outcomes of children, aged 9 years, whose mothers had UIC < 150 µg/L or > 150 µg/L during pregnancy. They concluded that children whose mothers had UIC < 150 µg/L showed reductions of 10.0% in spelling (- 41.1 points, CI -68.0 to - 14.3, p 0.003), 7.6% in grammar (- 30.9 points, CI - 60.2 to - 1.7, p 0.038), and 5.7% in English-literacy (- 0.33 points, CI -0.63 to - 0.03, p0.034) performance compared with children whose mothers' UICs were > 150 µg/L.

In contrast, four of the nine studies, no reported an association with child cognitive outcomes based on UIC. Murcia et al.[49] study, published in 2011, implemented Index and Psychomotor Development Index using the Bayley Scales of Infant Development at age 1 year old and no associations were found between UIC and Mental Development Index (MDI) and Psychomotor Development Index (PDI). In this study, for UIC < 100 µg/L and 150–249 µg/L respectively, the mean (SD, n) of MDI were 100 (13.3, 220), and 98.4(16, 165), p=0.5 respectively and the mean (SD, n) of PDI were 100.7 (14.7, 220), and 99.4 (15.2, 165), p=0.68 respectively. As Zhou et al. [37] assessed childhood neurodevelopment, using Bayley Scales of Infant and Toddler Development (Bayley-III) at 18 months and did not report association between UIC in pregnancy and Bayley-III outcomes. Similar data were observed by Ghassabian et al.[62], that evaluated non-verbal IQ and language comprehension when children were 6 years old and concluded that UIC < 150 µg/g creatinine was not associated with children's non-verbal IQ (adjusted OR 1.33, CI 0.92 to 1.93) and there was no relation between maternal UIC and children's language comprehension at 6 years.

Publication bias

Publication bias was investigated for preterm birth. In the funnel plot, the presence of asymmetries was not observed in any of them. Thus, the Egger test was performed, with a P -value of > 0.05 (Figure 14).

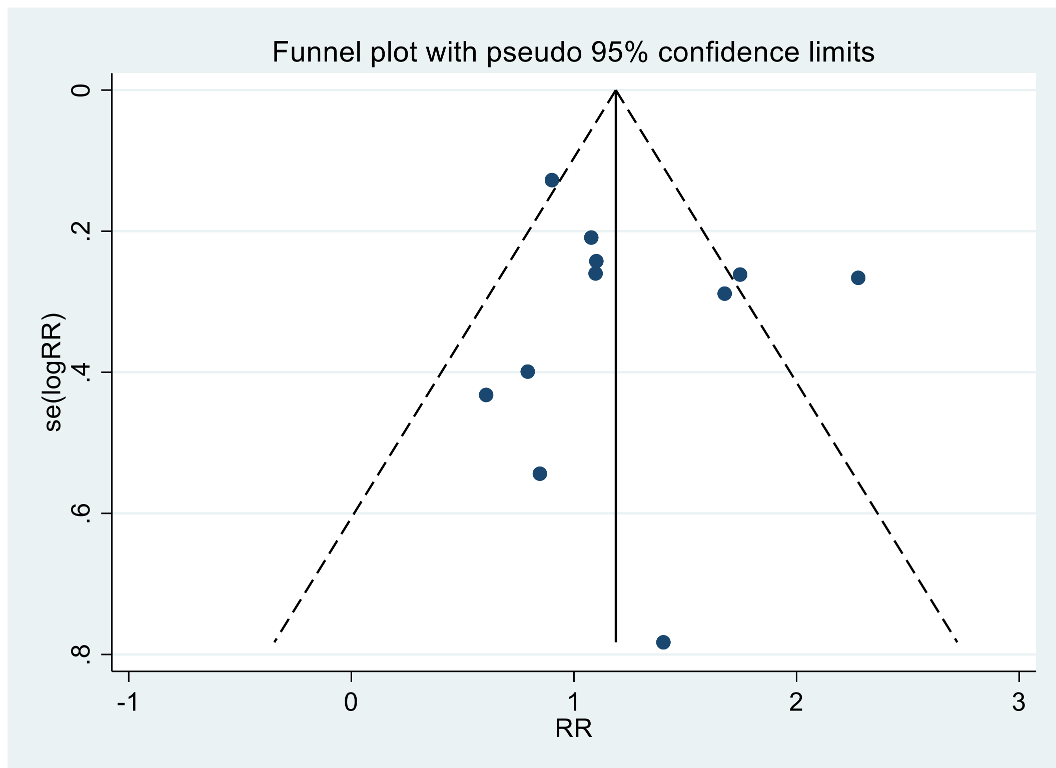

Figure 14. Preterm birth Funnel plot

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.
Number of studies =   11                              Root MSE      =   1.871
```

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	.9875945	.3354331	2.94	0.016	.228792	1.746397
bias	.8795722	1.33216	0.66	0.526	-2.133983	3.893128

```
Test of H0: no small-study effects          P = 0.526
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Discussion

In the current review, we evaluated the association of mean UIC (being the exposure UIC less than 150 µg/L and control UIC between 150-249 µg/L) in pregnancy with maternal and newborn outcomes. Forty-one studies were included in the meta-analysis, with a total of 36588 urine samples from pregnant women were assessed. The outcomes that were plotted in the meta-analyses were spontaneous miscarriage, hypothyroidism, subclinical hypothyroidism, maternal thyroid volume, maternal TSH measurement, preterm birth, stillbirth, low birthweight, small for gestational age, neonatal elevated TSH, birth length.

Most studies included showed no significant difference between UIC groups and the outcomes, however, some showed a significant difference between UIC < 150 µg/L and the outcome. The Charoenratana et al.[41] study, associated UIC < 150 µg/L with an increased risk of preterm birth and low birthweight and this was explained by the authors, by the prevalence of higher UIC < 150 µg/L than expected in the population evaluated and insufficiency of other nutritional factors in pregnant women. Gargari et al. [16] also observed an increase in preterm birth in the group with UIC < 150 µg/L, and the main influencing factors on maternal iodine deficiency, in this study, were weight gain during pregnancy, the interval between the most recent pregnancies, pregnancy unplanned, and no nutritional complement consumption.

Regarding low birthweight, Olivares et al. [50] assigned this outcome higher on UIC < 150 µg/L to low placental weight.

Both studies, from Nazarpour et al.[70] and Zhang et al.[17] , reported a significant difference in length at birth. The first one reported that this difference occurred due to collecting of urine samples on 3 different days of the week and may partially remove the bias and the second one reported that the sample was small.

Similar findings to our review were also concluded by other reviews. Nazeri et al. [71] analyzed mean birth weight, length, and head circumference values in newborns whose mothers had UIC < 150 or UIC > 150 µg/L during pregnancy and concluded that these anthropometric measures were not associated with maternal UIC during pregnancy. Another review, from Nazarpour et al.[72] showed no evidence of an association among the odds of preterm birth, low birth weight and hypertensive disorders of pregnancy in euthyroid pregnant women between UIC groups. Therefore, these results emphasize that no associations were found between UIC < 150 µg/L and maternal and neonatal outcomes. Regarding neurodevelopmental outcomes, the review from Monaghan et al.[73] also described similar data to our review and the lack of association in these studies could be explained by the different types of cognitive testing conducted and selected children with no matching ages.

Nevertheless, our review has some limitations. The main limitation is regarding the study design of the included studies, all of them are observational studies. Because of this, we could not evaluate the influence of the known and unknown confounders in the analyses. Another limitation is regarding the eligibility criteria, we elected as comparison groups UIC levels between 150 and 249 µg/L, however most studies classified them as being > 150 µg/L. We also could not plot neuromotor development and IQ scores data in the meta-analyses because assessment methods and ages were different. The confounders of each study, such as the maternal body mass index, age, education, occupation, ethnicity, parity, socioeconomic status, antibodies, are another limitation, which may be sources of the heterogeneity observed across the included studies. Another consideration, is that UIC reflects iodine intake over a short time and the intraindividual variation is huge; this may not be a reliable indicator of chronic iodine status.

Despite of these limitations, our review has the merit to make a synthesis of data regarding association between urinary iodine and maternal and infant outcomes.

It is important to emphasize that although we did not find a difference between the groups in the measured outcomes, as the certainty of evidence was low or very low a lack of statistical significance cannot be interpreted as no effect, especially due to the designs of the included studies. Additionally, it was not part of this review to discuss the need for iodine supplementation in pregnant women. Our main question was whether urinary iodine levels < 150 µg/L are associated with maternal and newborn outcomes. A question that can be raised after our results is if a UIC < 150 µg/L represents pregnant women with iodine insufficiency.

Regarding the measurement of urinary iodine, Vejbjerg et al. consider that the average value of spot urinary iodine concentration is a reliable measure of iodine intake in populations of at least 500 individuals [74].

Conclusion

In pregnant women, we did not find an association between UIC < 150 µg/L and the following maternal and newborn outcomes: spontaneous miscarriage, hypothyroidism, subclinical hypothyroidism, maternal thyroid volume, mean TSH, preterm birth, stillbirth, low birthweight, small for gestational age, neonatal elevated TSH, birth length. For neuromotor development and IQ scores, a narrative description was made due to the impossibility of performing meta-analysis for these outcomes; some studies showed an association and others not.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Shi X, Han C, Li C, et al. Optimal and Safe Upper Limits of Iodine Intake for Early Pregnancy in Iodine-Sufficient Regions: A Cross-Sectional Study of 7190 Pregnant Women in China. Journal of Clinical Endocrinology and Metabolism 2015;100(4):1630–1638; doi: 10.1210/jc.2014-3704.
2. Harding KB, Peña-Rosas JP, Webster AC, et al. Iodine Supplementation for Women during the Preconception, Pregnancy and Postpartum Period. Cochrane Database of Systematic Reviews 2017; 3(3):CD011761; doi: 10.1002/14651858.CD011761.pub2.
3. Rohner F, Zimmermann M, Jooste P, et al. Biomarkers of Nutrition for Development-Iodine Review. J Nutr 2014; 144(8):1322S-1342S; doi: 10.3945/jn.113.181974.
4. Glinoer D. The Regulation of Thyroid Function in Pregnancy: Pathways of Endocrine Adaptation from Physiology to Pathology. Endocr Rev 1997;18(3):404-433; doi: 10.1210/edrv.18.3.0300.
5. Dunn JT. Iodine Supplementation and the Prevention of Cretinism. Ann N Y Acad Sci 1993;678:158-168; doi: 10.1111/j.1749-6632.1993.tb26119.x.
6. Andersson M, de Benoist B, Delange F, et al. Prevention and Control of Iodine Deficiency in Pregnant and Lactating Women and in Children Less than 2-Years-Old: Conclusions and Recommendations of the Technical Consultation. In: Public Health Nutrition Cambridge University Press; 2007; pp. 1606–1611; doi: 10.1017/S1368980007361004.
7. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. In: Joanna Briggs Institute Reviewer's Manual. (Aromataris E, Munn Z. eds.). The Joanna Briggs Institute: 2017. Available from https://reviewersmanual.joannabriggs.org/.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. J Clin Epidemiol 2009;62(10):e1-34; doi: 10.1016/j.jclinepi.2009.06.006.
9. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a Web and Mobile App for Systematic Reviews. Syst Rev 2016;5(1); doi: 10.1186/s13643-016-0384-4.

10. Hozo SP, Djulbegovic B, Hozo I. Estimating the Mean and Variance from the Median, Range, and the Size of a Sample. BMC Med Res Methodol 2005;5; doi: 10.1186/1471-2288-5-13.
11. Riley RD, Higgins JP, Deeks JJ. Interpretation of Random Effects Meta-Analyses. BMJ 2011;342:d549; doi: 10.1136/bmj.d549.
12. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Intervention. Second. Chichester (UK): John Wiley & Sons; 2019.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-926; doi: 10.1136/bmj.39489.470347.AD.
14. Schiller T, Agmon A, Ostrovsky V, et al. Moderate Iodine Deficiency Is Common in Pregnancy but Does Not Alter Maternal and Neonatal Thyroid Function Tests. Front Endocrinol (Lausanne) 2020;11; doi: 10.3389/fendo.2020.523319.
15. Silva De Morais N, Ayres Saraiva D, Corcino C, et al. Consequences of Iodine Deficiency and Excess in Pregnancy and Neonatal Outcomes: A Prospective Cohort Study in Rio de Janeiro, Brazil. Thyroid 2020;30(12):1792–1801; doi: 10.1089/thy.2019.0462.
16. Gargari SS, Fateh R, Bakhshali-Bakhtiari M, et al. Maternal and Neonatal Outcomes and Determinants of Iodine Deficiency in Third Trimester of Pregnancy in an Iodine Sufficient Area. BMC Pregnancy Childbirth 2020;20(1); doi: 10.1186/s12884-020-02863-6.
17. Zhang X, Yuan N, Sun J, et al. Association Between Iodine Nutritional Status and Adverse Pregnancy Outcomes in Beijing, China: A Single-Center Cohort Study. Biol Trace Elem Res 2021; doi: 10.1007/s12011-021-02887-9.
18. Abel MH, Korevaar TIM, Erlund I, et al. Iodine Intake Is Associated with Thyroid Function in Mild to Moderately Iodine Deficient Pregnant Women. Thyroid 2018;28(10):1359–1371; doi: 10.1089/thy.2018.0305.
19. Berg V, Nøst TH, Skeie G, et al. Thyroid Homeostasis in Mother-Child Pairs in Relation to Maternal Iodine Status: The MISA Study. Eur J Clin Nutr 2017;71(8):1002–1007; doi: 10.1038/ejcn.2017.83.
20. Chen R, Li Q, Cui W, et al. Maternal Iodine Insufficiency and Excess Are Associated with Adverse Effects on Fetal Growth: A Prospective Cohort Study in Wuhan, China. J Nutr 2018;148(11):1814–1820; doi: 10.1093/jn/nxy182.
21. Gyamfi D, Wiafe YA, Danquah KO, et al. Urinary Iodine Concentration and Thyroid Volume of Pregnant Women Attending Antenatal Care in Two Selected Hospitals in Ashanti Region, Ghana: A Comparative Cross-Sectional Study. BMC Pregnancy Childbirth 2018;18(1); doi: 10.1186/s12884-018-1820-3.
22. Hynes KL, Otahal P, Burgess JR, et al. Reduced Educational Outcomes Persist into Adolescence Following Mild Iodine Deficiency in Utero, despite Adequacy in Childhood: 15-Year Follow-Up of

the Gestational Iodine Cohort Investigating Auditory Processing Speed and Working Memory. Nutrients 2017;9(12); doi: 10.3390/nu9121354.

23. Kianpour M, Aminorroaya A, Amini M, et al. Thyroid-Stimulating Hormone (TSH) Serum Levels and Risk of Spontaneous Abortion: A Prospective Population-Based Cohort Study. Clin Endocrinol (Oxf) 2019;91(1):163–169; doi: 10.1111/cen.13979.
24. Koyuncu K, Turgay B and Söylemez F. Iodine Deficiency in Pregnant Women at First Trimester in Ankara. J Turk Ger Gynecol Assoc 2019;20(1):37–40; doi: 10.4274/jtgga.galenos.2018.2017.0150.
25. Levie D, Derakhshan A, Shu H, et al. The Association of Maternal Iodine Status in Early Pregnancy with Thyroid Function in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy Study. Thyroid 2019;29(11):1660–1668; doi: 10.1089/thy.2019.0164.
26. Markhus MW, Dahl L, Moe V, et al. Maternal Iodine Status Is Associated with Offspring Language Skills in Infancy and Toddlerhood. Nutrients 2018;10(9); doi: 10.3390/nu10091270.
27. Mioto VCB, Monteiro ACCNG, de Camargo RYA, et al. High Prevalence of Iodine Deficiency in Pregnant Women Living in Adequate Iodine Area. Endocr Connect 2018;7(5):762–767; doi: 10.1530/EC-18-0131.
28. Murcia M, Espada M, Julvez J, et al. Iodine Intake from Supplements and Diet during Pregnancy and Child Cognitive and Motor Development: The INMA Mother and Child Cohort Study. J Epidemiol Community Health 2018;72(3):216–222; doi: 10.1136/jech-2017-209830.
29. Nazarpour S, Ramezani Tehrani F, Amiri M, et al. Maternal Urinary Iodine Concentration and Pregnancy Outcomes: Tehran Thyroid and Pregnancy Study. Biol Trace Elem Res 2020;194(2):348–359; doi: 10.1007/s12011-019-01812-5.
30. Pan Z, Cui T, Chen W, et al. Serum Iodine Concentration in Pregnant Women and Its Association with Urinary Iodine Concentration and Thyroid Function. Clin Endocrinol (Oxf) 2019;90(5):711–718; doi: 10.1111/cen.13945.
31. Ruiz Ochoa D, Piedra León M, Lavín Gómez BA, et al. Influence of Iodine Status on Maternal Thyroid Function during Pregnancy. Endocrinol Diabetes Nutr 2017;64(6):331–333; doi: 10.1016/j.endien.2017.02.014.
32. Torlinska B, Bath SC, Janjua A, et al. Iodine Status during Pregnancy in a Region of Mild-to-Moderate Iodine Deficiency Is Not Associated with Adverse Obstetric Outcomes; Results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Nutrients 2018;10(3); doi: 10.3390/nu10030291.
33. Ulu H, Marakoğlu K, Akyürek F, et al. Evaluation of Urinary Iodine Levels and Thyroid Function Tests in Pregnant Women and Their Infants. Acta Endocrinol 2017;13(1):47–52; doi: 10.4183/aeb.2017.47.

34. Xiao Y, Sun H, Li C, et al. Effect of Iodine Nutrition on Pregnancy Outcomes in an Iodine-Sufficient Area in China. Biol Trace Elem Res 2018;182(2):231–237; doi: 10.1007/s12011-017-1101-4.
35. Yang J, Liu Y, Liu H, et al. Associations of Maternal Iodine Status and Thyroid Function with Adverse Pregnancy Outcomes in Henan Province of China. J Trace Element Med Biol 2018;47:104–110; doi: 10.1016/j.jtemb.2018.01.013.
36. Zhang Y, Du C, Wang W, et al. Effect of Maternal and Neonatal Factors on Neonatal Thyroid Stimulating Hormone: Results from a Population-Based Prospective Cohort Study in China. J Trace Element Med Biol 2018;49:151–156; doi: 10.1016/j.jtemb.2018.05.008.
37. Zhou SJ, Condo D, Ryan P, et al. Association between Maternal Iodine Intake in Pregnancy and Childhood Neurodevelopment at Age 18 Months. Am J Epidemiol 2019;188(2):332–338; doi: 10.1093/aje/kwy225.
38. Alvarez-Pedrerol M, Guxens M, Mendez M, et al. Iodine Levels and Thyroid Hormones in Healthy Pregnant Women and Birth Weight of Their Offspring. Eur J Endocrinol 2009;160(3):423–429; doi: 10.1530/EJE-08-0716.
39. Amouzegar A, Khazan M, Hedayati M, et al. An Assessment of the Iodine Status and the Correlation between Iodine Nutrition and Thyroid Function during Pregnancy in an Iodine Sufficient Area. Eur J Clin Nutr 2014;68(3):397–400; doi: 10.1038/ejcn.2013.273.
40. Bath SC, Steer CD, Golding J, et al. Effect of Inadequate Iodine Status in UK Pregnant Women on Cognitive Outcomes in Their Children: Results from the Avon Longitudinal Study of Parents and Children (ALSPAC). The Lancet 2013;382(9889):331–337; doi: 10.1016/S0140-6736(13)60436-5.
41. Charoenratana C, Leelapat P, Traisrisilp K, et al. Maternal Iodine Insufficiency and Adverse Pregnancy Outcomes. Matern Child Nutr 2016;12(4):680–687; doi: 10.1111/mcn.12211.
42. Cho YY, Kim HJ, Soo-Young O, et al. Iodine Status in Healthy Pregnant Women in Korea: A First Report. Eur J Nutr 2016;55(2):469–475; doi: 10.1007/s00394-015-0864-7.
43. Delshad H, Touhidi M, Abdollahi Z, et al. Inadequate Iodine Nutrition of Pregnant Women in an Area of Iodine Sufficiency. J Endocrinol Invest 2016;39(7):755–762; doi: 10.1007/s40618-016-0438-4.
44. Habimana L, Twite KE, Daumerie C, et al. High Prevalence of Thyroid Dysfunction among Pregnant Women in Lubumbashi, Democratic Republic of Congo. Thyroid 2014;24(3):568–575; doi: 10.1089/thy.2013.0261.
45. Hynes KL, Otahal P, Hay I, et al. Mild Iodine Deficiency during Pregnancy Is Associated with Reduced Educational Outcomes in the Offspring: 9-Year Follow-up of the Gestational Iodine Cohort. J Clin Endocrinol Metabol 2013;98(5):1954–1962; doi: 10.1210/jc.2012-4249.

46. Medici M, Ghassabian A, Visser W, et al. Women with High Early Pregnancy Urinary Iodine Levels Have an Increased Risk of Hyperthyroid Newborns: The Population-Based Generation R Study. Clin Endocrinol (Oxf) 2014;80(4):598–606; doi: 10.1111/cen.12321.
47. Mills JL, Mehnaz A, Louis GMB, et al. Pregnancy Loss and Iodine Status: The LIFE Prospective Cohort Study. Nutrients 2019;11(3); doi: 10.3390/nu11030534.
48. Moreno-Reyes R, Glinoer D, Oyen HV, et al. High Prevalence of Thyroid Disorders in Pregnant Women in a Mildly Iodine-Deficient Country: A Population-Based Study. J Clini Endocrinol Metabol 2013;98(9):3694–3701; doi: 10.1210/jc.2013-2149.
49. Murcia M, Rebagliato M, Iñiguez C, et al. Effect of Iodine Supplementation during Pregnancy on Infant Neurodevelopment at 1 Year of Age. Am J Epidemiol 2011;173(7):804–812; doi: 10.1093/aje/kwq424.
50. Olivares JL, Olivi GI, Verdasco C, et al. Low Iodine Intake during Pregnancy. Endocrinol Nutr 2012;59(5):326–330; doi: 10.1016/j.endoen.2011.12.001.
51. Rebagliato M, Murcia M, Álvarez-Pedrerol M, et al. Iodine Supplementation during Pregnancy and Infant Neuropsychological Development. Am J Epidemiol 2013;177(9):944–953; doi: 10.1093/aje/kws333.
52. Rebagliato M, Murcia M, Espada M, et al. Iodine Intake and Maternal Thyroid Function during Pregnancy. Epidemiology 2010;21(1):62–69; doi: 10.1097/EDE.0b013e3181c1592b.
53. Ruiz AM, Martínez EG, Rodríguez MÁR, et al. Yododeficiencia En Mujeres Gestantes Del Área Sanitaria de Palencia (España). Endocrinol Nutr 2009;56(10):452–457; doi: 10.1016/S1575-0922(09)73313-3.
54. Rydbeck F, Rahman A, Grand´er M, et al. Maternal Urinary Iodine Concentration up to 1.0 Mg/L Is Positively Associated with Birth Weight, Length, and Head Circumference of Male Offspring. J Nutr 2014;144(9):1438-1444; doi: 10.3945/jn.114.193029.
55. Soldin OP, Tractenberg RE and Pezzullo JC. Do Thyroxine and Thyroid-Stimulating Hormone Levels Reflect Urinary Iodine Concentrations? Ther Drug Monit 2005;27(2):178-185; doi: 10.1097/01.ftd.0000149954.20089.0b.
56. Vila L, Legaz G, Barrionuevo C, et al. Iodine status and thyroid volume changes during pregnancy: results of a survey in Aran Valley (Catalan Pyrenees). Endocrinol Invest 2008;31(10):851-855; doi: 10.1007/BF03346430.
57. Yoganathan T, Hettiarachchi M, Arasaratnam V, et al. Maternal Iodine Status and the Thyroid Function of Pregnant Mothers and Their Neonates in Jaffna District of Sri Lanka. Indian J Endocrinol Metab 2015;19(6):817–823; doi: 10.4103/2230-8210.167563.
58. Saraiva DA, Morais NA de O e. S de, Martins Corcino C, et al. Iodine Status of Pregnant Women from a Coastal Brazilian State after the Reduction in Recommended Iodine Concentration in Table

Salt According to Governmental Requirements. Nutrition 2018;53:109–114; doi: 10.1016/j.nut.2018.02.001.

59. Corcino CM, Berbara TMBL, Saraiva DA, et al. Variation of Iodine Status during Pregnancy and Its Associations with Thyroid Function in Women from Rio de Janeiro, Brazil. Public Health Nutr 2019;22(7):1232–1240; doi: 10.1017/S1368980019000399.
60. Rajatanavin R. Iodine Deficiency in Pregnant Women and Neonates in Thailand. Public Health Nutr 2007;10(12A):1602-1605; doi: 10.1017/S1368980007360990.
61. Azizi F and Malboosbaf R. Long-Term Antithyroid Drug Treatment: A Systematic Review and Meta-Analysis. Thyroid 2017;27(10):1223–1231; doi: 10.1089/thy.2016.0652.
62. Ghassabian A, Steenweg-de Graaff J, Peeters RP, et al. Maternal Urinary Iodine Concentration in Pregnancy and Children's Cognition: Results from a Population-Based Birth Cohort in an Iodine-Sufficient Area. BMJ Open 2014;4(6):e005520; doi: 10.1136/bmjopen-2014-005520.
63. Yang L, Li M, Liu X, et al. Evaluation of Iodine Nutritional Status among Pregnant Women in China. Thyroid 2020;30(3):443–450; doi: 10.1089/thy.2019.0001.
64. Guo M, Yu Z, Yao J, et al. Thyroid Structure, Function and Iodine Status by Pregnancy Trimester in Harbin, China. Asia Pac J Clin Nutr 2020;29(4):789–794; doi: 10.6133/apjcn.202012_29(4).0014.
65. Guo W, Wang W, Jin Y, et al. Trimester-Specific Thyroid Function in Pregnant Women with Different Iodine Statuses. Ann Nutr Metab 2020;76(3):165–174; doi: 10.1159/000506276.
66. Cui X, Yu H, Wang Z, et al. No Association Was Found Between Mild Iodine Deficiency During Pregnancy and Pregnancy Outcomes: A Follow-up Study Based on a Birth Registry. Biol Trace Elem Res 2022; doi: 10.1007/s12011-021-03028-y.
67. Kampouri M, Tofail F, Rahman SM, et al. Gestational and Childhood Urinary Iodine Concentrations and Children's Cognitive Function in a Longitudinal Mother-Child Cohort in Rural Bangladesh. Int J Epidemiol 2022; doi: 10.1093/ije/dyac110.
68. Wang T, Liu Y, Kong Q, et al. Effect of Moderate-to-Severe Iodine Deficiency in Early Pregnancy on Subclinical Hypothyroidism: A Longitudinal Study in an Iodine-Sufficient Region in China. Front Nutr 2022;9; doi: 10.3389/fnut.2022.839651.
69. Oguz Kutlu A and Kara C. Iodine Deficiency in Pregnant Women in the Apparently Iodine-Sufficient Capital City of Turkey. Clin Endocrinol (Oxf) 2012;77(4):615–620; doi: 10.1111/j.1365-2265.2012.04440.x.
70. Nazarpour S, Ramezani Tehrani F, Amiri M, et al. Maternal Urinary Iodine Concentration and Pregnancy Outcomes: Tehran Thyroid and Pregnancy Study. Biol Trace Elem Res 2020;194(2):348–359; doi: 10.1007/s12011-019-01812-5.

71. Nazeri P, Shab-Bidar S, Pearce EN, et al. Do Maternal Urinary Iodine Concentration or Thyroid Hormones within the Normal Range during Pregnancy Affect Growth Parameters at Birth? A Systematic Review and Meta-Analysis. Nutr Rev 2020;78(9):747–763; doi: 10.1093/nutrit/nuz105.
72. Nazarpour S, Ramezani Tehrani F, Behboudi-Gandevani S, et al. Maternal Urinary Iodine Concentration and Pregnancy Outcomes in Euthyroid Pregnant Women: A Systematic Review and Meta-Analysis. Biol Trace Elem Res 2020;197(2):411–420; doi: 10.1007/s12011-019-02020-x.
73. Monaghan AM, Mulhern MS, McSorley EM, et al. Associations between Maternal Urinary Iodine Assessment, Dietary Iodine Intakes and Neurodevelopmental Outcomes in the Child: A Systematic Review. Thyroid Res 2021;14(1); doi: 10.1186/s13044-021-00105-1.
74. Vejbjerg P, Knudsen N, Perrild H, et al. Estimation of Iodine Intake from Various Urinary Iodine Measurements in Population Studies. Thyroid 2009;19(11):1281–1286; doi: 10.1089/thy.2009.0094.

Supporting Information

S1. Search Strategies

Medline and CENTRAL-Cochrane Strategies:

Search on the Medline (Pubmed) and CENTRAL-Cochrane platforms:

#1 “Iodine"[Mesh] OR (Iodine-127) OR (Iodine 127) OR (Urinary Iodine) OR (Iodine deficient) OR (Iodine deficiency) OR (Iodine sufficient) OR (Iodine levels) OR (Levels of iodine) OR (Iodine sources) OR (Iodine status) OR (Iodine stores) OR (Iodine concentration) OR (Iodine intake) OR (Intake of iodine) OR (Urine iodine concentration) OR (Urinary iodine concentration) OR (Renal iodide clearance) OR (Median urinary iodine concentration) OR (Urinary iodine excretion) OR (24-hour urinary iodine excretion) OR (Urinary iodine) OR (Urinary iodine analysis) OR (urinary iodine testing) OR (Dosage of iodine) OR (Loss of iodine) OR (Urinary iodine values) OR (Iodine-containing supplements) OR (Iodine supplementation) OR (Iodine supplement) OR (Supplementary iodine intake) OR (Iodine nutrition) OR (Status of iodine nutrition) OR (Iodine nutritional status) OR (Iodine metabolism) OR (Thyroid iodide clearance) OR (Absolute iodide uptake) OR (Oral load of iodine) OR (Iodine-rich food) OR (Dietary iodine intake) OR (Dietary iodine sources) OR (Dietary iodine requirement) OR (Salt iodization) OR (Iodized salt) OR (Iodine/day) OR (Level of Iodine Intake) OR (Iodine deficient area) OR (Iodine-sufficient area) OR (Iodine-sufficient populations) OR (Fetal iodine requirements)
#2 "Pregnancy"[Mesh] OR (Pregnancies) OR (Gestation) OR (Maternal Iodine) OR (Pregnant women) OR (Pregnant) OR (Lactating women) OR (Maternal iodine status) OR (Maternal iodine intake) OR (Postpartum) OR (Pregnant patient)

Embase Strategy

Search on the Embase (Elsevier) platform:

#1 'iodine'/exp OR '127 I' OR '127 I iodine' OR '127 iodine' OR '127I' OR 'hormonal iodine' OR 'I 127' OR 'inorganic iodine' OR 'iod sol' OR 'iodine 127' OR 'iodine I 127' OR 'iodine isotope' OR 'iodine isotopes' OR 'iodine mixture' OR 'iodine solution' OR 'iodine tincture' OR 'iodium' OR 'iosal' OR 'J 127' OR 'jodium' OR 'medadine' OR 'neo hydriol fluid' OR 'neo hydriol viscous' OR 'sublimed iodine' OR 'tincture of iodine' OR ‘iodine-127’ OR ‘iodine 127’ OR ‘urinary iodine’ OR ‘iodine deficient’ OR ‘iodine deficiency’ OR ‘iodine sufficient’ OR ‘iodine levels’ OR ‘levels of iodine’ OR ‘iodine sources’ OR ‘iodine status’ OR ‘iodine stores’ OR ‘iodine concentration’ OR ‘iodine intake’ OR ‘intake of iodine’ OR ‘urine iodine concentration’ OR ‘urinary iodine concentration’ OR ‘renal iodide clearance’ OR ‘median urinary iodine

concentration’ OR ‘urinary iodine excretion’ OR ‘24-hour urinary iodine excretion’ OR ‘urinary iodine’ OR ‘urinary iodine analysis’ OR ‘urinary iodine testing’ OR ‘dosage of iodine’ OR ‘loss of iodine’ OR ‘urinary iodine values’ OR ‘iodine-containing supplements’ OR ‘iodine supplementation’ OR ‘iodine supplement’ OR ‘supplementary iodine intake’ OR ‘iodine nutrition’ OR ‘status of iodine nutrition’ OR ‘iodine nutritional status’ OR ‘iodine metabolism’ OR ‘thyroid iodide clearance’ OR ‘absolute iodide uptake’ OR ‘oral load of iodine’ OR ‘iodine-rich food’ OR ‘dietary iodine intake’ OR ‘dietary iodine sources’ OR ‘dietary iodine requirement’ OR ‘salt iodization’ OR ‘iodized salt’ OR ‘iodine/day’ OR ‘level of Iodine Intake’ OR ‘iodine deficient area’ OR ‘iodine-sufficient area’ OR ‘iodine-sufficient populations’ OR ‘fetal iodine requirements’

#2 'pregnancy'/exp OR 'child bearing' OR 'childbearing' OR 'gestation' OR 'gravidity' OR 'intrauterine pregnancy' OR 'labor presentation' OR 'labour presentation' OR 'pregnancy maintenance' OR 'pregnancy trimesters' OR ‘pregnancies’ OR ‘maternal iodine’ OR ‘pregnant women’ OR ‘pregnant’ OR ‘lactating women’ OR ‘maternal iodine status’ OR ‘maternal iodine intake’ OR ‘postpartum’ OR ‘pregnant patient’

LILACS Strategy

Search on the LILACS (BVS) platform:

#1 MH:”Iodo” OR (Iodo-127) OR MH:D01.268.380.400$ OR MH:SP4.011.097.063.999$ OR MH:SP4.021.202.133.794.825$

2 MH:”Gravidez“ OR (Gestação) OR MH:G08.686.784.769$

S2. References from studies not included

1. Castillo C, Lustig N, Margozzini P, et al. Thyroid-Stimulating Hormone Reference Ranges in the First Trimester of Pregnancy in an Iodine-Sufficient Country. Endocrinol Metab (Seoul) 2018;33(4):466-472; doi: 10.3803/EnM. 2018.33.4.466.
2. Chaudhary LN, Khatiwada S, Geal B, et al. Iodine and Thyroid Function Status, and Anti-thyroid Peroxidase Antibody among Pregnant Women in Eastern Nepal. J Nepal Health Res Counc 2017;15(2):114-119; doi: 10.3126/jnhrc. v15i2.18182.
3. Cuellar-Rufino S, Navarro-Meza M, García-Solís P, et al. Iodine levels are associated with oxidative stress and antioxidant status in pregnant women with hypertensive disease. Nutr Hosp 2017;34(3):661-666; doi: 10.20960/ nh.460.

4. De Zoysa E, Hettiarachchi M, Liyanage C. Urinary iodine and thyroid determinants in pregnancy: a follow up study in Sri Lanka. BMC Pregnancy Childbirth 2016;16(1):303; doi: 10.1186/s12884-016-1093-7.
5. Dold S, Zimmermann MB, Jukic T, et al. Universal Salt Iodization Provides Sufficient Dietary Iodine to Achieve Adequate Iodine Nutrition during the First 1000 Days: A Cross-Sectional Multicenter Study. J Nutr 2018;148(4): 587-598; doi: 10.1093/jn/nxy015.
6. Farebrother J, Zimmermann MB, Abdallah F, et al. Effect of Excess Iodine Intake from Iodized Salt and/or Groundwater Iodine on Thyroid Function in Nonpregnant and Pregnant Women, Infants, and Children: A Multicenter Study in East Africa. Thyroid 2018;28(9):1198-1210; doi: 10.1089/thy. 2018.0234.
7. Fereja M, Gebremedhin S, Gebreegziabher T, et al. Prevalence of iodine deficiency and associated factors among pregnant women in Ada district, Oromia region, Ethiopia: a cross-sectional study. BMC Pregnancy Childbirth 2018;18(1):257; doi: 10.1186/s12884-018-1905-z.
8. Henjum S, Aakre I, Lilleengen AM, et al. Suboptimal Iodine Status among Pregnant Women in the Oslo Area, Norway. Nutrients 2018;10(3):280; doi: 10.3390/nu10030280.
9. Hess SY, Ouédraogo CT, Young RR, et al. Urinary iodine concentration identifies pregnant women as iodine deficient yet school-aged children as iodine sufficient in rural Niger. Public Health Nutr 2017;20(7):1154-1161; doi: 10.1017/S1368980016003232.
10. Hu LY, Zhu CH, Su MF, et al. [Urinary iodine concentration status and its influencing factors of pregnant women in Yuhuan county, Zhejiang Province]. Zhonghua Yu Fang Yi Xue Za Zhi 2018;52(1):85-87; doi: 10.3760/cma.j.issn. 0253-9624.2018.01.016.
11. Ozberk DI, Kutlu R, Kilinc I, et al. Effects of mandatory salt iodization on breast milk, urinary iodine concentrations, and thyroid hormones: is iodine deficiency still a continuing problem?J Endocrinol Invest 2019;42(4):411-418; doi: 10.1007/s40618-018-0930-0.
12. Ollero MD, Toni M, Pineda JJ, et al. Thyroid Function Reference Values in Healthy Iodine-Sufficient Pregnant Women and Influence of Thyroid Nodules on Thyrotropin and Free Thyroxine Values.Thyroid 2019;29(3):421-429; doi: 10.1089/thy.2018.0324.
13. Ren IT, Jia QZ, Zhang XD, et al. [Prevalence of thyroid function in pregnant and lactating women in areas with different iodine levels of Shanxi province]. Zhonghua Liu Xing Bing Xue Za Zhi. 2018;39(5):609-613; doi: 10.3760/cma.j. issn.0254-6450.2018.05.013.
14. Renaguli A, Luo YZ, Wang XL, et al. [Relationship between thyrotropin and urine iodine in Han and Uygur nationalities pregnancy women in People's Hospital of Xinjiang Uygur Autonomous Region]. Zhonghua Fu Chan Ke Za Zhi. 2018;53(9):595-601; doi: 10.3760/cma.j.issn.0529-567x.2018.09.003.

15. Restini LAO, Dessordi R, Ferreira SMS, et al. Assessment of thyroid function, ioduria and oxidative stress in women in the first trimester of pregnancy. Nutr Hosp 2018;35(6):1387-1393; doi: 10.20960/nh.1653.
16. Snart CJP, Keeble C, Taylor E, et al. Maternal Iodine Status and Associations with Birth Outcomes in Three Major Cities in the United Kingdom. Nutrients 2019;11(2):441; doi: 10.3390/nu11020441.
17. Stinca S, Andersson M, Herter-Aeberli I, et al. Moderate-to-Severe Iodine Deficiency in the "First 1000 Days" Causes More Thyroid Hypofunction in Infants Than in Pregnant or Lactating Women. J Nutr 2017;147(4):589-595; doi: 10.3945/jn.116.244665.
18. Wang K, Zhang J, Li F, et al. Urinary iodine in early pregnancy is associated with subclinical hypothyroidism in Tianjin, China: an observational study. BMC Endocr Disord 2017;17(1):10; doi: 10.1186/s12902-017-0162-x.
19. Zhang D, Cai K, Wang G, et al. Trimester-specific reference ranges for thyroid hormones in pregnant women. Medicine (Baltimore) 2019;98(4):e14245; doi: 10.1097/MD.0000000000014245.
20. Ardawi MSM, Nasrat HA, Mustafa BE. Urinary iodine excretion and maternal thyroid function. During pregnancy and postpartum. Saudi Med J 2002; 23(4):413-22.
21. Azizi F, Aminorroya A, Hedayati M, et al. Urinary iodine excretion in pregnant women residing in areas with adequate iodine intake. Public Health Nutr 2003;6(1):95-8; doi: 10.1079/PHN2002366.
22. Blumenthal N, Byth K, Eastman CJ. Iodine Intake and Thyroid Function in Pregnant Women in a Private Clinical Practice in Northwestern Sydney before Mandatory Fortification of Bread with Iodised Salt. Thyroid Res 2012;2012:798963; doi: 10.1155/2012/798963.
23. Celik H, Guldiken S, Celik O, et al. Iodine deficiency in pregnant women living in western turkey (edirne). Acta Endocrinol (Buchar) 2016;12(1):14-18; doi: 10.4183/aeb.2016.14.
24. Chakraborty I, Chatterjee S, Bhadra D, et al. Iodine deficiency disorders among the pregnant women in a rural hospital of West Bengal. Indian J Med Res 2006;123(6):825-829.
25. Chakraborty I, Mazumdar P, Chakraborty PS, et al. Iodine deficiency disorder among pregnant women in a tertiary care hospital of Kolkata, India. Southeast Asian J Trop Med Public Health 2010;41(4):989-995.
26. Chen W, Sang Z, Tan L, et al. Neonatal thyroid function born to mothers living with long-term excessive iodine intake from drinking water. Clin Endocrinol (Oxf) 2015;83(3):399-404; doi: 10.1111/cen.12625.

27. Chinyanga EA, Chidede O, Machisvo A, et al. Urinary iodine excretion in pregnant women as an index of the impact of a national iodization programme. Cent Afr J Med. 2006;52(7-8):78-83; doi: 10.4314/cajm.v52i7-8.62585.
28. Costeira MJ, Oliveira P, Ares S, et al. Iodine status of pregnant women and their progeny in the Minho Region of Portugal. Thyroid 2009;19(2):157-163; doi: 10.1089/thy.2008.0249.
29. Das SC, Isichei UP, Mohammed AZ, et al. Impact of iodine deficiency on thyroid function in pregnant African women - A possible factor in the genesis of 'small for dates' babies. Indian J Clin Biochem 2005;20(2):35-42; doi: 10.1007/ BF02867398.
30. Domínguez I, Reviriego S, Rojo-Martínez G, et al. Iodine deficiency and thyroid function in healthy pregnant women. Med Clin (Barc) 2004;122(12):449-453; doi: 10.1016/s0025-7753(04)74269-4.
31. Elahi S, Rizvi NB, Nagra SA. Iodine deficiency in pregnant women of Lahore. J Pak Med Assoc. 2009;59(11):741-743.
32. Elnagar B, Eltom A, Wide L, et al. Iodine status, thyroid function and pregnancy: study of Swedish and Sudanese women. J Clin Nutr 1998;52(5): 351-355; doi: 10.1038/sj.ejcn.1600563.
33. Eltom A, Elnagar B, Elbagir M, et al. Thyroglobulin in serum as an indicator of iodine status during pregnancy. Scand J Clin Lab Invest 2000;60(1):1-7; doi: 10.1080/00365510050184985.
34. Eltom A, Elnagar B, Gebre-Medhin M. Thyroid hormones and iodine status in Sudanese pregnant women with goitre. Int J Food Sci Nutr 1999;50(2):105-109; doi: 10.1080/096374899101292.
35. Fister P, Gaberscek S, Zaletel K, et al. Thyroid volume changes during pregnancy and after delivery in an iodine-sufficient Republic of Slovenia. Eur J Obstet Gynecol Reprod Biol. 2009;145(1):45-48; doi: 10.1016/j.ejogrb. 2009.03.022.
36. Fuse Y, Shishiba Y, Irie M. Gestational changes of thyroid function and urinary iodine in thyroid antibody-negative Japanese women. Endocr J 2013;60(9): 1095-1096; doi: 10.1507/endocrj.ej13-0184.
37. Gietka-Czernel M, Dębska M, Kretowicz P, et al. Iodine status of pregnant women from central Poland ten years after introduction of iodine prophylaxis programme. Endokrynol Pol 2010;61(6):646-651.
38. Mateo MCG, Fernández MF, Revenga VV, et al. Assessment of iodine nutritional status and thyroxine levels in pregnant women from different geographic areas of the Castile and Leon. Endocrinol Nutr 2011;58(8):416-421; doi: 10.1016/j.endonu.2011.05.014.
39. Gowachirapant S, Melse-Boonstra A, Winichagoon P, et al. Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. Matern Child Nutr 2014;10(1):61-71; doi: 10.1111/mcn. 12040.

40. Grau G, Aguayo A, Vela A, et al. Normal intellectual development in children born from women with hypothyroxinemia during their pregnancy. J Trace Elem Med Biol 2015;31:18-24; doi: 10.1016/j.jtemb.2015.02.004.
41. Guan H, Li C, Li Y, et al. High iodine intake is a risk factor of post-partum thyroiditis: result of a survey from Shenyang, China. Endocrinol Invest 2005;28(10):876-881; doi: 10.1007/BF03345318.
42. Gunnarsdottir I, Gustavsdottir AG, Steingrimsdottir L, et al. Iodine status of pregnant women in a population changing from high to lower fish and milk consumption. Public Health Nutr 2013;16(2):325-329; doi: 10.1017/ S1368980012001358.
43. Habimana L, Twite KE, Wallemacq P, et al. Iodine and iron status of pregnant women in Lubumbashi, Democratic Republic of Congo. Public Health Nutr 2013;16(8):1362-1370; doi: 10.1017/S1368980012005484.
44. Hess SY, Zimmermann MB, Torresani T, et al. Monitoring the adequacy of salt iodization in Switzerland: a national study of school children and pregnant women. Eur J Clin Nutr 2001;55(3):162-166; doi: 10.1038/sj.ejcn.1601140.
45. Hiéronimus S, Bec-Roche M, Ferrari P, et al. Iodine status and thyroid function of 330 pregnant women from Nice area assessed during the second part of pregnancy. Ann Endocrinol (Paris) 2009;70(4):218-224; doi: 10.1016/j.ando. 2009.03.004.
46. Jaiswal N, Melse-Boonstra A, Sharma SK, et al. The iodized salt programme in Bangalore, India provides adequate iodine intakes in pregnant women and more-than-adequate iodine intakes in their children. Public Health Nutr 2015;18(3):403-413; doi: 10.1017/S136898001400055X.
47. Jaiswal N, Melse-Boonstra A, Thomas T, et al. High prevalence of maternal hypothyroidism despite adequate iodine status in Indian pregnant women in the first trimester. Thyroid 2014;24(9):1419-1429; doi: 10.1089/thy.2014. 0071.
48. Jaruratanasirikul S, Chukamnerd J, Koranantakul O, et al. The relationship of maternal iodine status and neonatal thyrotropin concentration: a study in Southern Thailand. J Pediatr Endocrinol Metab 2006;19(5):727-732; doi: 10.1515/jpem.2006.19.5.727.
49. Jaruratanasirikul S, Sangsupawanich P, Koranantakul O, et al. Maternal iodine status and neonatal thyroid-stimulating hormone concentration: a community survey in Songkhla, southern Thailand. Public Health Nutr 2009;12(12):2279-2284; doi: 10.1017/S1368980009005205.
50. Joshi K, Nair S, Khade C, et al. Early gestation screening of pregnant women for iodine deficiency disorders and iron deficiency in urban centre in Vadodara, Gujarat, India. J Dev Orig Health Dis 2014;5(1):63-68; doi: 10.1017/S2040174413000470.

51. Kapil U, Pandey RM, Sareen N, et al. Iodine nutritional status in Himachal Pradesh state, India. J Endocrinol Metab. 2015;19(5):602-607; doi: 10.4103/ 2230-8210.163173.
52. Kapil U, Sareen N, Nambiar VS, et al. Status of iodine nutrition among pregnant mothers in selected districts of Uttarakhand, India. J Endocrinol Metab. 2015;19(1):106-109. doi: 10.4103/2230-8210.131764.
53. Konrade I, Kalere I, Strele I, et al. Iodine deficiency during pregnancy: a national cross-sectional survey in Latvia. Public Health Nutr 2015;18(16): 2990-2997; doi: 10.1017/S1368980015000464.
54. Korenek A, Prochazka M. Iodine in early pregnancy--is there enough? Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2008;152(1):97-99; doi: 10.5507/bp.2008.015.
55. Korevaar TI, Chaker L, Jaddoe VW, et al. Maternal and Birth Characteristics Are Determinants of Offspring Thyroid Function. J Clin Endocrinol Metab 2016;101(1):206-213; doi: 10.1210/jc.2015-3559.
56. Korevaar TIM, Schalekamp-Timmermans S, Rijke YB, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab 2013;98(11):4382-4390; doi: 10.1210/jc.2013-2855.
57. Kung AWC, Chau MT, Lao TT, et al. The effect of pregnancy on thyroid nodule formation. J Clin Endocrinol Metab 2002;87(3):1010-1014; doi: 10.1210/ jcem.87.3.8285.
58. Kung AW, Lao TT, Chau MT, et al. Goitrogenesis during pregnancy and neonatal hypothyroxinaemia in a borderline iodine sufficient area. Clin Endocrinol (Oxf) 2000;53(6):725-731; doi: 10.1046/j.1365-2265.2000. 01156.x.
59. Kurtoglu S, Akcakus M, Kocaoglu C, et al. Iodine status remains critical in mother and infant in Central Anatolia (Kayseri) of Turkey. Eur J Nutr 2004;43(5):297-303; doi: 10.1007/s00394-004-0474-2.
60. Kurtoğlu S, Akcakuş M, Kocaoğlu C, et al. Iodine deficiency in pregnant women and in their neonates in the central Anatolian region (Kayseri) of Turkey. Turk J Pediatr 2004;46(1):11-15.
61. Kut A, Gursoy A, Senbayram S, et al. Iodine intake is still inadequate among pregnant women eight years after mandatory iodination of salt in Turkey. J Endocrinol Invest 2010;33(7):461-464; doi: 10.1007/BF03346625.
62. Lean MI, Lean ME, Yajnik CS, et al. Iodine status during pregnancy in India and related neonatal and infant outcomes. Public Health Nutr. 2014;17(6):1353-1362; doi: 10.1017/S1368980013001201.
63. León G, Murcia M, Rebagliato M, et al. Maternal thyroid dysfunction during gestation, preterm delivery, and birthweight. The Infancia y Medio Ambiente Cohort, Spain. Paediatr Perinat Epidemiol 2015;29(2):113-122; doi: 10.1111/ ppe.12172.

64. Lola L. Study links iodine deficiency in pregnancy with poor cognitive outcomes in children. BMJ 2013;346:f3365; doi: 10.1136/bmj.f3365.
65. Luton D, Alberti C, Vuillard E, et al. Iodine deficiency in northern Paris area: impact on fetal thyroid mensuration. PLoS One 2011;6(2):e14707; doi: 10.1371/journal.pone.0014707.
66. McElduff A, McElduff P, Gunton JE, et al. Neonatal thyroid-stimulating hormone concentrations in northern Sydney: further indications of mild iodine deficiency? Med J Aust 2002;176(7):317-320; doi: 10.5694/j.1326-5377.2002.tb04431.x.
67. Torre EM, Alvarez ED, Artal AR, et al. Iodine nutrition in pregnant women from Oviedo area. Is iodine supplementation necessary? Endocrinol Nutr 2014;61(8):404-409; doi: 10.1016/j.endonu.2014.02.005.
68. Meng F, Zhao R, Liu P, et al. Assessment of iodine status in children, adults, pregnant women and lactating women in iodine-replete areas of China. PLoS One 2013;8(11):e81294; doi: 10.1371/journal.pone.0081294.
69. Menon KC, Skeaff SA, Thomson CD, et al. The effect of maternal iodine status on infant outcomes in an iodine-deficient Indian population. Thyroid 2011;21(12):1373-1380; doi: 10.1089/thy.2011.0130.
70. Mezosi E, Molnar I, Jakab A, et al. Prevalence of iodine deficiency and goitre during pregnancy in east Hungary. Eur J Endocrinol 2000;143(4):479-483; doi: 10.1530/eje.0.1430479.
71. Moleti M, Trimarchi F, Tortorella G, et al. Effects of Maternal Iodine Nutrition and Thyroid Status on Cognitive Development in Offspring: A Pilot Study. Thyroid 2016;26(2):296-305; doi: 10.1089/thy.2015.0336.
72. Olivares JL, Ortiz VA, Mayer M, et al. An approach to a sanitary and social problem: urinary iodine excretion in pregnant women from a iodine deficient region. Arch Latinoam Nutr 2009;59(4):378-382.
73. Orito Y, Oku H, Kubota S, et al. Thyroid function in early pregnancy in Japanese healthy women: relation to urinary iodine excretion, emesis, and fetal and child development. J Clin Endocrinol Metab 2009;94(5):1683-1688; doi: 10.1210/jc.2008-2111.
74. Peris BR, Calvo FR, Tenias JMB, et al. Iodine deficiency and pregnancy. Current situation. Endocrinol Nutr 2009;56(1):9-12. doi: 10.1016/S1575-0922(09) 70188-3.
75. Pettigrew-Porter A, Skeaff S, Gray A, et al. Are pregnant women in New Zealand iodine deficient? A cross-sectional survey. Aust N Z J Obstet Gynaecol 2011;51(5):464-467; doi: 10.1111/j.1479-828X.2011.01331.x.
76. Rezvanian H, Aminorroaya A, Majlesi M, et al. Thyroid size and iodine intake in iodine-repleted pregnant women in Isfahan, Iran. Endocr Pract 2002;8(1):23-28; doi: 10.4158/EP.8.1.23.

77. Sánchez-Vega J, del Rey FE, Fariñas-Seijas H, et al. Inadequate iodine nutrition of pregnant women from Extremadura (Spain). Eur J Endocrinol 2008;159(4): 439-445; doi: 10.1530/EJE-08-0309.
78. Sekitani Y, Hayashida N, Takahashi J, et al. Urinary iodine concentrations of pregnant women in Ukraine. Clin Chem Lab Med 2013;51(4):811-816; doi: 10.1515/cclm-2012-0397.
79. Soares R, Vanacor R, Manica D, et al. Thyroid volume is associated with family history of thyroid disease in pregnant women with adequate iodine intake: a cross-sectional study in southern Brazil. J Endocrinol Invest 2008;31(7):614-617; doi: 10.1007/BF03345612.
80. Rodríguez MS, San Julián CA, de Aguilar VA. Iodine intake during pregnancy: effects on thyroid function in mother and child. Endocrinol Nutr 2013;60(7):352-357; doi: 10.1016/j.endonu.2013.01.010.
81. Travers CA, Guttikonda K, Norton CA, et al. Iodine status in pregnant women and their newborns: are our babies at risk of iodine deficiency? Med J Aust2006;184(12):617-620; doi: 10.5694/j.1326-5377.2006.tb00417.x.
82. Velasco I, Martín J, Gallego M, et al. Maternal-fetal thyroid function at the time of birth and its relation with iodine intake. Thyroid 2013;23(12):1619-1626; doi: 10.1089/thy.2013.0035.
83. Vermiglio F, Lo Presti VP, Castagna MG, et al. Increased risk of maternal thyroid failure with pregnancy progression in an iodine deficient area with major iodine deficiency disorders. Thyroid 1999;9(1):19-24; doi: 10.1089/thy.1999.9.19.
84. Wang Y, Dou Y, Zhu X, et al. A comparative study on iodine nutrition and thyroid function of different population in urban and rural areas of Wuwei, Gansu province. Zhonghua Liu Xing Bing Xue Za Zhi 2015;36(10):1095-1098.
85. Wang Y, Zhang Z, Ge P, et al. Iodine status and thyroid function of pregnant, lactating women and infants (0-1 yr) residing in areas with an effective Universal Salt Iodization program Asia Pac J Clin Nutr 2009;18(1):34-40.
86. Wang Y, Ge P, Ma Q, et al. Study on the relationship between iodine status and growth in infants at the key period of brain development. Zhonghua Yi Xue Za Zhi 2012;33(2):164-167.
87. Wei Z, Wang W, Zhang J, et al. Urinary iodine level and its determinants in pregnant women of Shanghai, China. Br J Nutr 2015;113(9):1427-1432; doi: 10.1017/S0007114515000665.
88. Zhang Y, Liu F, Sun W, et al. Establishment of reference ranges for thyroid-related indicators in normal pregnant women. Zhonghua Yi Xue Za Zhi 2016;96(5):339-343; doi: 10.3760/cma.j.issn.0376-2491.2016.05.005.
89. Zimmermann MB, Aeberli I, Torresani T, et al. Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study. Am J Clin Nutr 2005;82(2):388-392; doi: 10.1093/ajcn.82.2.388.

90. Zou S, Wu F, Guo C, et al. Iodine nutrition and the prevalence of thyroid disease after salt iodization: a cross-sectional survey in Shanghai, a coastal area in China. PLoS One 2012;7(7):e40718; doi: 10.1371/journal.pone. 0040718.
91. Chinyanga EA, Dako DY. Profile of thyroid function and urinary iodine excretion of pregnant women attending Harare Central Hospital antenatal clinic. Cent Afr J Med 1989;35(5):396-400.
92. Dodd NS, Madan J. Iodine status in pregnancy. Asia Pac J Clin Nutr 1993; 2(3):119-123
93. Filteau SM, Sullivan KR, Anwar US, et al. Iodine deficiency alone cannot account for goitre prevalence among pregnant women in Modhupur, Bangladesh. Eur J Clin Nutr 1994;48(4):293-302.
94. Gaitan E, Cooksey RC, Meydrech EF, et al. Thyroid function in neonates from goitrous and nongoitrous iodine-sufficient areas. J Clin Endocrinol Metab 1989;69(2):359-363; doi: 10.1210/jcem-69-2-359.
95. Pedersen KM, Börlum KG, Knudsen PR, et al. Urinary iodine excretion is low and serum thyroglobulin high in pregnant women in parts of Denmark. Acta Obstet Gynecol Scand 1988;67(5):413-416; doi: 10.3109/ 00016348809004251.
96. Smyth PP, Hetherton AM, Smith DF, et al. Maternal iodine status and thyroid volume during pregnancy: correlation with neonatal iodine intake. J Clin Endocrinol Metab 1997;82(9):2840-2843; doi: 10.1210/jcem.82.9.4203.
97. Lee YA, Cho SW, Sung HK, et al. Effects of Maternal Iodine Status during Pregnancy and Lactation on Maternal Thyroid Function and Offspring Growth and Development: A Prospective Study Protocol for the Ideal Breast Milk Cohort. Endocrinol Metab (Seoul) 2018;33(3):395-402; doi: 10.3803/EnM. 2018.33.3.395.
98. Lim KK, Chan YY, Teh CH, et al. Iodine status among pregnant women in rural Sabah, Malaysia. Asia Pac J Clin Nutr 2017;26(5):861-866; doi: 10.6133/apjcn. 092016.06.
99. Brucker-Davis F, Ferrari P, Gal J, et al. Iodine status has no impact on thyroid function in early healthy pregnancy. J Thyroid Res. 2012;2012:168764; doi: 10.1155/2012/168764.
100. Brucker-Davis F, Ferrari P, Gal J, et al. Iodine status of pregnant and postpartum Japanese women: effect of iodine intake on maternal and neonatal thyroid function in an iodine-sufficient area. J Clin Endocrinol Metab 2011;96(12):3846-3854; doi: 10.1210/jc.2011-2180.
101. Lean MI, Lean ME, Yajnik CS, et al. Iodine status during pregnancy in India and related neonatal and infant outcomes. Public Health Nutr. 2014;17(6): 1353-1362, doi: 10.1017/S1368980013001201.
102. Li H, Wang Y, Zheng J, et al. Analysis on iodine nutritional status and thyroid function in pregnant women. Wei Sheng Yan Jiu 2012;41(4):532-535.

103. Marco A, Vicente A, Castro E, et al. Patterns of iodine intake and urinary iodine concentrations during pregnancy and blood thyroid-stimulating hormone concentrations in the newborn progeny. Thyroid 2010;20(11):1295-1299; doi: 10.1089/thy.2010.0046.
104. Ojule AC, Osotimehin BO. Maternal and neonatal thyroid status in Saki, Nigeria. Afr J Med Med Sci 1998;27(1-2):57-61.
105. Riaño Galán I, Martínez PS, Díaz MPM, et al. Psycho-intellectual development of 3 year-old children with early gestational iodine deficiency. J Pediatr Endocrinol Metab 2005;18 Suppl 1:1265-1272; doi: 10.1515/jpem.2005. 18.s1.1265.
106. Shi L, Tian Y, Piao J, et al. Iodine nutritional status of pregnant, lactating women and children in Linxia Region of Gansu Province. Wei Sheng Yan Jiu 2002;31(4):282-284.
107. Wang Y, SunW, Zhu X, et al. Changes of iodine nutrition status and thyroid function among pregnant women in iodine sufficient rural area of Gansu province. Zhonghua Liu Xing Bing Xue Za Zhi 2014;35(1):49-52.
108. Wang Y, Ge P, Wang G, et al. Study on the status of nutrition in pregnant women, lactating women and babies in Yongjing, Gansu province. Zhonghua Liu Xing Bing Xue Za Zhi 2008;29(3):258-261.
109. Zhou R, Tao Y, Dong X, et al. Study on the relation between iodine nutrition of pregnant women in different occasions and thyroid function of their neonates. Zhonghua Liu Xing Bing Xue Za Zhi 2002;23(5):356-359.
110. van Mil NH, Tiemeier H, Bongers-Schokking JJ, et al. Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. J Nutr 2012;142(12):2167-2174; doi: 10.3945/jn. 112.161950.
111. Cromie KJ, Threapleton DE, Snart CJP, et al. Maternal iodine status in a multi-ethnic UK birth cohort: associations with autism spectrum disorder. BMC Pediatr 2020;20(1):544; doi: 10.1186/s12887-020-02440-y.
112. Threapleton DE, Snart CJP, Keeble C, et al. Maternal iodine status in a multi-ethnic UK birth cohort: Associations with child cognitive and educational development. Paediatr Perinat Epidemiol. 2021;35(2):236-246; doi: 10.1111/ ppe.1271.