Subclinical Hypothyroidism ASRM Practice Guideline

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Disclosures:

Views are my own and do not represent the official policy of the NIH, DHHS, US Army, DoD, ASRM, SART, USF, or SGF

Chair of the ASRM document

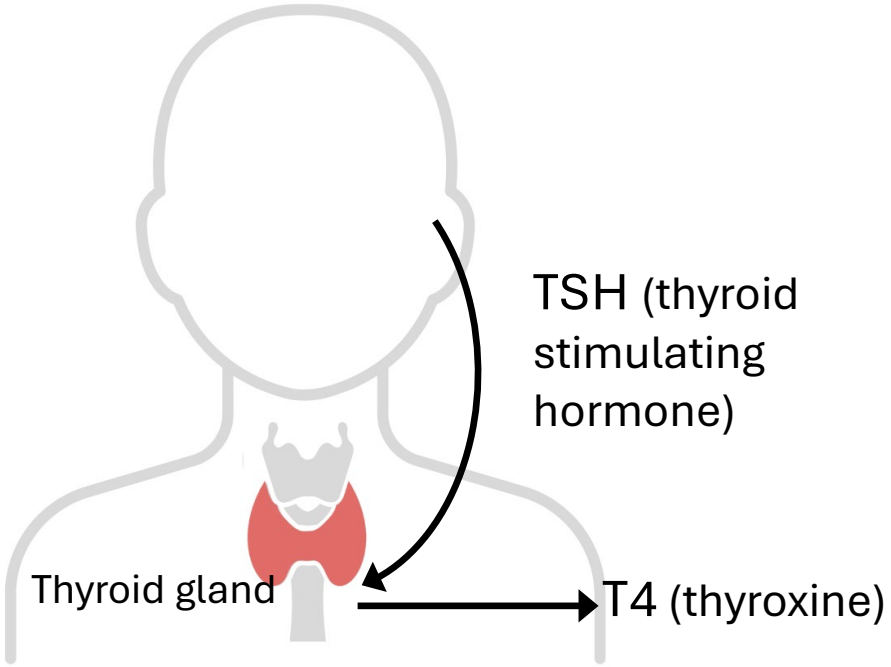
Acknowledgements:

Dr. Leigh Ann Humphries

Subclinical Hypothyroidism

Historical Perspective

Subclinical hypothyroidism



Overt hypothyroidism

- Elevated TSH
- Low T4
- Often symptomatic

0.2-0.3% of reproductive age population

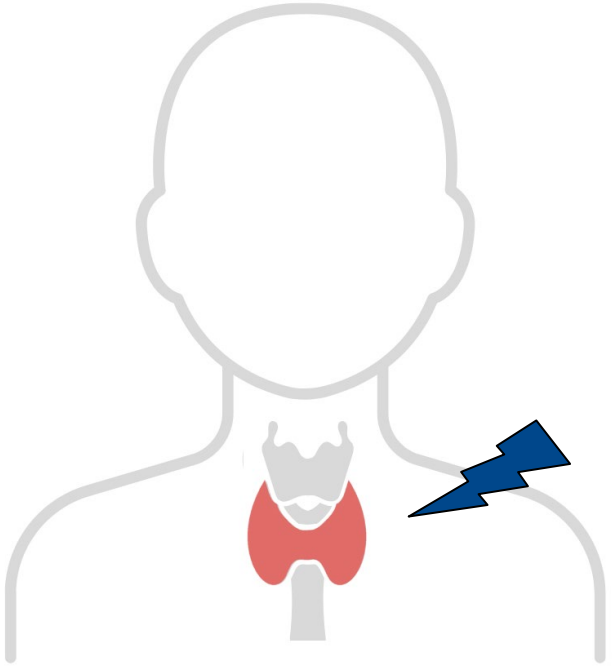
Subclinical hypothyroidism

- Elevated TSH
- Normal T4
- Asymptomatic

4-8% of reproductive age population

Hollowell et al. 2002
Aoki et al. 2007
Canaris et al. 2000

Thyroid autoimmunity



Anti-TPO (anti-thyroid peroxidase)

Anti-Tg (anti-thyroglobulin)

Presence of Anti-TPO and anti-Tg antibodies in the serum

- 2-17% of pregnant women
- 12.5% of the U.S. population

Causally implicated in Hashimoto's

- Anti-thyroid antibodies attack thyroid tissue, causing progressive fibrosis

Alexander et al. 2017
Consortium JAMA 2019
Spencer et al. 2007

Elevated TSH Definitions

Non-pregnant individuals:

Laboratory-specific range (97.5th percentile)

Reproductive-age population (12-49 years, NHANES 1999-2002): 4.4 mIU/L

Disease-free U.S. population (NHANES 1988-1994): 4.12 mIU/L

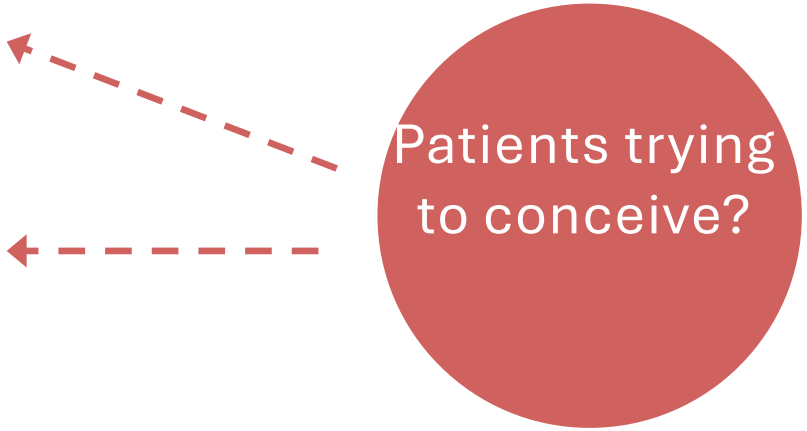
Most common in literature: 4-5 mIU/L

Pregnant individuals:

1st trimester: 2.5 mIU/L

2nd trimester: 3.0 mIU/L

3rd trimester: 3.0 mIU/L



Aoki et al. 2007
Hollowell et al. 2002
Groot et al. 2012
Soldin et al. 2004
Dashe et al. 2005

Overt Hypothyroidism and Adverse Outcomes

Overt hypothyroidism in pregnancy →

Preterm birth	(OR 1.34, 99% CI 1.17–1.53)
Preeclampsia	(OR 1.47, 99% CI 1.20–1.81)
Superimposed preeclampsia	(OR 2.25, 99% CI 1.53–3.29)
Gestational diabetes	(OR 1.57, 99% CI 1.33–1.86)
Cesarean delivery after labor	(OR 1.38, 99% CI 1.14–1.66)
Intensive care unit admission	(OR 2.08, 99% CI 1.04–4.15)

Miscarriage and fetal death	(smaller observational studies)
Low birth weight	
Postpartum hemorrhage	
Placental abruption	
Neurocognitive impairment in newborn/child	

Mannisto et al. 2013
Consortium on Safe Labor: 223,512 pregnancies among 204,180 women (3,183 with hypothyroidism)

Origins of TSH > 2.5 mIU/L

#1: National Association of Clinical Biochemistry (NACB) in 2003

- “more than 95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mIU/L.”

Baloch et al. 2003
Hollowell et al. 2002

#2: Theory that treatment of TSH >2.5 mU/L would prevent progression to overt hypothyroidism

- TSH levels >2.0 mIU/L are associated with overt hypothyroidism, particularly in those with antithyroid antibodies.

Vanderpump et al. 1995
Huber et al. 2002

Other Guidelines

American Thyroid Association

2011:
If diagnosed hypothyroidism, goal TSH <2.5 prior to conception

2017:
Insufficient data in women trying to conceive
However, may treat “to prevent progression to overt hypothyroidism” and because “low-dose 25–50 mcg carries minimal risk”

American Society for Reproductive Medicine

2015:
It is controversial whether to use first-trimester pregnancy threshold (TSH >2.5 mIU/L) to diagnose and treat SCH in women attempting pregnancy

ASRM has never advocated for the use of lower TSH cutoffs or for the treatment of SCH in patients trying to conceive

Stagnaro-Green et al. 2011
Alexander et al. 2017
ASRM 2015

SCH progression to overt hypothyroidism

The Whickham Survey

- Newcastle upon Tyne, UK: 2779 adults from 1972-1974
- 20-year follow-up
  TSH > 6mIU/L: OR 8 (95% CI 3-20)
  Antithyroid antibodies: OR 8 (95% CI 5-15)
  TSH > 6 mIU/L and antibodies: OR 38 (22-65)

- High rate of “hypothyroidism” overall: 7.7%.

Inflection point at TSH 2.0 mIU/L

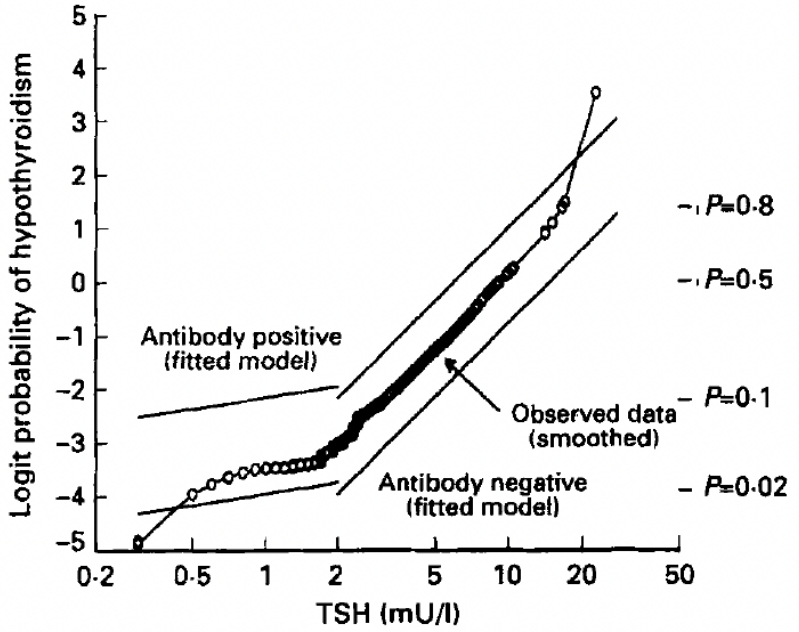
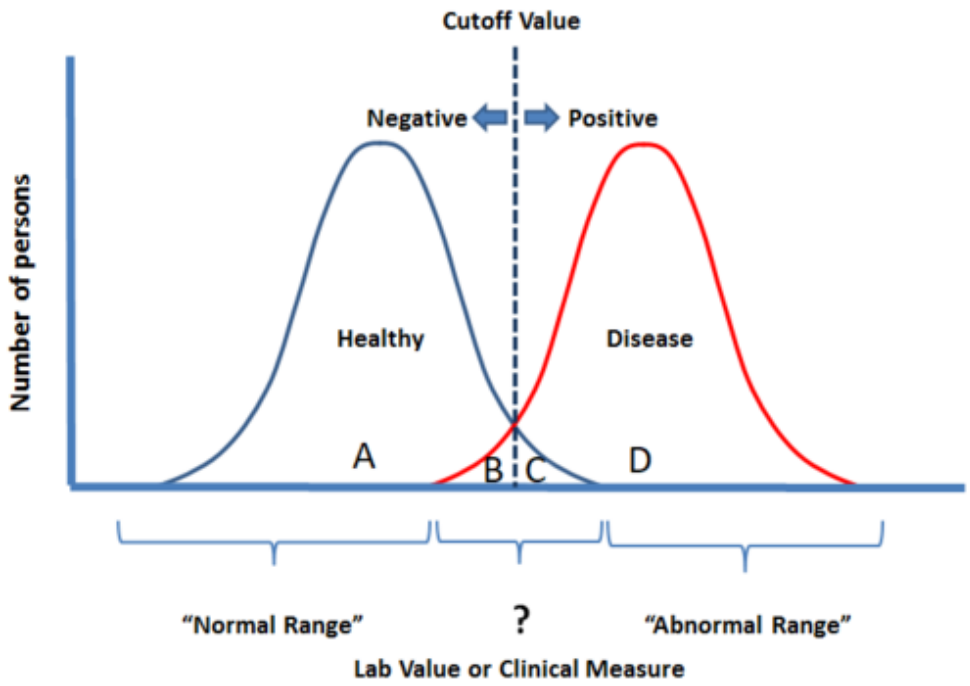


Fig. 4 Logit probability (log odds) for development within twenty years of hypothyroidism with increasing values of TSH as measured at first survey in 912 female survivors. $\log\{P/(1-P)\} = b_0 + b_1 \ln \text{TSH} + 0{\cdot}27$ age $(+1{\cdot}79$ if antibody + ve). $b_0 = -5{\cdot}02$, $b_1 = 0{\cdot}30$ if TSH < 2 mU/l; $b_0 = -6{\cdot}38$, $b_1 = 1{\cdot}97$ if TSH $\geqslant 2$ mU/l.

Vanderpump et al. 1995

SCH is, by definition, a laboratory diagnosis with arbitrary cutoffs



Which cutoff has greatest clinical significance?

Could treating SCH at lower cutoffs improve fertility and pregnancy outcomes and prevent progression to overt hypothyroidism?

Lowering cutoff to <2.5 mIU/L would result in almost 20% of the U.S. population diagnosed with SCH (and up to 30% of those undergoing IVF)

Introduction Take Home Points

1. Overt hypothyroidism is associated with adverse reproductive outcomes

2. Population percentiles have been used to define SCH

3. TSH > 2.5 mIU/L historic origins lies in
    1. Population 95th percentile
    2. Pregnancy recommendations for overt hypothyroidism
    3. Risk of long-term progression from normal or SCH to overt hypothyroidism

Practice Committee

Scientific Literature

Key standards and principles for developing evidence-based clinical guidelines: balancing health professional, patient, funder, and government needs

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Clinical practice guidelines are critical tools to inform healthcare decision-making, yet development faces significant challenges ensuring rigorous, reliable, and globally applicable recommendations. This review examines the essential standards and evolving proaches for creating high-quality, evidence-based guidelines that can effectively support clinical practice across diverse healthc settings. Key standards for high-quality clinical practice guideline development emerge from leading global health organizatio emphasizing several critical components—establishing a multidisciplinary development group, defining a clear and relevant scope, c ducting systematic evidence reviews and meta-analyses, and ensuring transparency throughout the development process. Innovat principles address emerging challenges such as research integrity assessment, incorporation of patient-centered methodologies, pron tion of global collaborative approaches, and development of strategic implementation strategies. These evolving principles recogn the complex landscape of modern healthcare, where guidelines should adhere to rigorous standards to genuinely improve patient o comes and encourage best practice care across diverse healthcare settings. (Fertil Steril® 2025;123:561–8. ©2025 by American Soci for Reproductive Medicine.)

Key Words: Guidelines, evidence-based, research integrity, guideline development, patient-centered care

Clinical practice guidelines (CPGs) are systematically developed statements designed to assist clinicians, patients, and policymakers to make well-informed healthcare decisions regarding the screening, diagnosing, monitoring and management of health conditions (1–4). Historically, CPGs began taking shape in the 1970s through initiatives such as the National Institutes of Health Consensus Development Program, where expert panels formulate recommendations on the basis of personal experience and selective references, with limited integration of scientific evidence or systematic appraisal (3, 5). However, the rise of evidence-based medicine in the 1980s and 1990s fundamentally _reshaped CPGs, prioritizing rigorously appraised research evidence over expert opinion alone (3, 5).

Today, CPG development represents a major undertaking, involving comprehensive systematic reviews, careful _synthesis of evidence, and transparent structured approach to decision-making. This process, although essential for quality, is resource-intensive and time-consuming. Nevertheless, many regional organizations around the world continue to publish independent guidelines. The rise in local CPG development has introduced challenges, particularly in terms of resource demands, duplicated efforts, and the production of multiple CPGs of often poor quality and conflicting recommendations (2, 6–8). In women's health, a prominent example is the variation in polycystic ovary syndrome (PCOS) diagnostic criteria across guidelines from the American Society for Reproductive Medicine (ASRM), European Society of Human Reproduction and Embryology (ESHRE), the Androgen Excess and Polycystic

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Clinical practice guidelines for reproductive health care

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Amidst the rapidly changing landscape of diagnosis and management in reproductive medicine, it has become increasingly difficult to evaluate the usefulness of many clinical practices. Clinical practice guidelines are a way to incorporate the best evidence-based research with clinical experience, cost-effectiveness, and patient demands. However, there may be problems with the development, maintenance, and implementation of such guidelines. This series of papers describes existing guidelines in the American Society for Reproductive Medicine and internationally and provides clinician comments on how they should be used. (Fertil Steril® 2025;123:551–2. ©2025 by American Society for Reproductive Medicine.)

Key Words: Evidence-based medicine, clinical guidelines, IVF, infertility

In the distant past, a wise clinician could garner all the knowledge and experience available and make individual decisions about treatment without recourse to others or professional societies. That is no longer the case, because our research knowledge expands exponentially and nonmedical factors in society increasingly influence our independence and decisions about risk. We are controlled by rules and regulations to protect our patients, our institutions, and ourselves from harm while seeking the best quality reproductive care for the community. Some of this is controlled by government and state legislation imposed outside of the medical system, but much is generated by our desire to provide a safe and effective health service for our patients in an environment where medical care is increasingly patient-focused, expensive, complicated, and interdisciplinary. Whether it is the hospital we work in, our professional society, or the medical reimbursement scheme on which we depend, we are continually reminded of how we should practice in a responsible and safe manner. Failure to follow this advice may open us to legal, financial, and reputational risk. The brilliant individual clinician meme is now apparently to be replaced by the obedient, law-abiding administrator of sensible, safe medicine. Can we continue to practice high-quality reproductive medicine based on the best available evidence and opinion in an environment where we still have the freedom to deliver sensible, individually inspired, common-sense health care for patients with variable complex needs?

I would suggest that this is possible using high-quality, professionally developed clinical practice guidelines. Most professions and their societies have distributed these advice-based documents to their members, and the American Society for Reproductive Medicine (ASRM) certainly has many. Clinical guidelines are supposed to be systematically developed recommendations or protocols to assist clinical providers in providing diagnosis, treatment, and care of patients (1). They are based on the best available scientific evidence, clinical expertise, and patient preferences developed by experts in the field, professional societies, or outside health agencies. They are often used to allocate resources an
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How does American Society for Reproductive Medicine produce clinical guidelines?

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American Society for Reproductive Medicine develops evidence-based practice guidelines through a rigorous process of identifying clinically significant questions, conducting systematic literature reviews, and evaluating evidence quality. The evidence-based recommendations in American Society for Reproductive Medicine practice guidelines provide reproductive healthcare professionals with standardized, scientifically grounded recommendations to enhance patient care. (Fertil Steril® 2025;123:553–60. ©2025 by American Society for Reproductive Medicine.)

Key Words: Guidelines, systematic review, ASRM

Founded in 1944, the American Society for Reproductive Medicine (ASRM) (then called the American Society for the Study of Sterility) has focused on sharing scientific advancements in reproduction with its members (1). During the first few decades, dissemination was accomplished through scientific meetings, postgraduate courses, and newsletters. In the 1980s, a committee of experts in the field was assembled by the Society to create guidance on reproductive technologies for this rapidly evolving field (2). These documents were based on expert consensus and covered a wide range of topics, including assisted reproductive technology, reproductive surgery, contraception, early pregnancy loss, and menopause (2).

In 2010, ASRM began to produce documents on the basis of principles from the Agency for Healthcare Research and Quality, Council of Medical Special Societies, and Institutes of Medicine and sought inclusion of the resulting documents in the National Guideline Clearinghouse. The first guideline developed using these rigorous methods, including a systematic review and literature grading, was the document titled "Mature oocyte cryopreservation a guideline" (3). This first ASRM guideline was impactful in the field because it established oocyte cryopreservation as the standard of care based on new randomized clinical trials demonstrating comparable live birth rates compared with fresh oocytes. Over time, the guideline development process has been refined for efficiency and congruence with guideline best practices. The rubrics used to evaluate strength of evidence for individual articles, strength of the body of evidence, and confidence in and strength of recommendation statements are informed by accepted principles of guideline development and other guideline development approaches (4–6). Current guideline development is described in this article on the basis of the standards set by the National Academy of Medicine and ECRI Guidelines Trust (7).

TYPES OF DOCUMENTS

Currently, the ASRM Practice Committee produces 2 primary document types, Guidelines and Committee Opinions, intended to provide evidence-based guidance to reproductive health practitioners. Topics for ASRM practice documents are selected to address gaps in available recommendations and reflect advancements in the field. ASRM considers suggestions from its members, committee members, and the ASRM Board of Directors, who provide insight into areas where guidance is needed. Additionally, ASRM conducts reviews to identify topics with newly published data, ensuring that its recommendations reflect the most up-to-date scientific evidence. The organization also seeks topics in which there is a lack of clinical consensus, prioritizing these areas to help provide clarity and establish standards.

Once a topic is chosen by the Practice Committee, the proposed document is evaluated for suitability to develop as a guideline or committee opinion (Table 1). This decision is based in part on the quality and quantity of the available evidence, as well as the scope of the proposed document. Although guidelines are based on targeted, narrow scientific questions with a

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How do health professionals react to clinical guidelines? Grit to cope with unpredictable situations and limitations not addressed by guidelines

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Assisted reproductive technology has become the primary treatment of infertility. As such, assisted reproductive technology has been regulated by certain authorities and primarily, structured by various scientific organisms through recommendations and guidelines. Yet, these have limits—the topic addressed here—and may at times need to rely on grit for managing the totally unexpected. Doctors should also cope with what is not addressed by these guidelines, including the couple's desire for final family size. (Fertil Steril® 2025;123:569–72. ©2025 by American Society for Reproductive Medicine.)

Key Words: Guidelines, assisted reproductive medicine, practice committee recommendation, resilience, protocol

ecade has seen a
new guidelines in all
ains of our specialty
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ese intend to list all
done—the dos and
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Reproduction. Guidelines are generally written in simple style—often by bullet point lists of recommendations—and are as comprehensive in a given field as possible. Comprehensiveness often involves large amounts of expert-based opinion given the limited level I evidence to support most recommendations in reproductive medicine. These expert opinions can be an anchor to progress because they are assiduously followed rather than questioned and challenged through proper studies. As medicine changes and expands rapidly, particularly in our field, guidelines are commonly renewed periodically; however, their information may still be outdated at the time of use, given the difficulty in real-time updating of individual recommendations. Often varying guidelines contradict themselves and ignore some important considerations for deciding the best management possible, including for example the final family size—final number of children—desired by the couple. Guidelines can also not cover rare or unpredictable presentations or events, in which case grit, a mixture of passion and perseverance over time (as described in Angela Duckworth's best-selling book Grit: The Power of Passion and Perseverance (1)), emerges as the guiding force.

THE LIMITS OF GUIDELINES AND CALL FOR GRIT: FROM AVIATION TO MEDICINE

The principle of medical guidelines is to outline all the measures that need to be taken in any given situation that we may encounter, so that cases are managed adequately. The safety concern that animates the processes of guideline writing is highly laudable. It can be compared with check lists and sets of standard operation procedures that have been accompanying other industries and, notably, aviation

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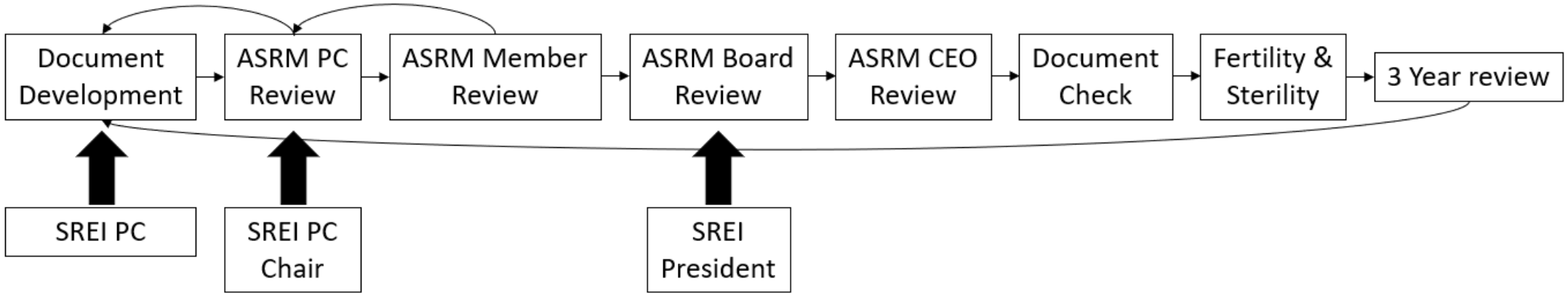
Iterative Practice Committee Process



Started in 2020 → Published in 2024

Task Force Composition

- Consulting epidemiologist - Suleena Kalra, MD, MSCE
- Chair- Good Shepherd from ASRM Practice Committee
- Members
  - Alex Quaas- CREST Scholar
  - Torie Plowden, Jennifer Eaton, Barry Witt, Mary Ellon Pavone- SREI PC
  - Karthryn Goldrick- Young member
- ASRM staff:
  - Zac Knight/Jeff Hayes, PhDs, Practice Initiatives and Guidelines Specialist
  - Jessica Goldstein, RN, Education Program Coordinator

Opinion versus Guideline

A guideline document follows a rigorous process that is based on the standards set by the National Academy of Medicine and ECRI Guidelines Trust and follows PICO framework

Committee opinions and guidance documents are documents produced by the Practice or Ethics Committees of ASRM that are NOT based on a systematic review and that do not follow the process as referenced above

What's in a guideline?

Includes:

- Complete description of databases searched
- Inclusion/exclusion criteria
- Assessment of the included literature
- Description of the quality of included articles
- Summary statements
- Strength of recommendations
- Conclusions, unanswered questions, and areas for future research
- Overall summary and recommendations sections
- Acknowledgment of task force members in acknowledgments section

Quality of Evidence

Quality of Evidence	Definition
High Quality	✓ Target population clearly identified ✓ Sufficient sample size for the study design ✓ Clear description of study design ✓ Appropriate control(s) ✓ Generalizable results ✓ Definitive conclusions ✓ **Minimal risk of bias** ✓ Limitations do not invalidate conclusions ✓ **Evidence primarily based on well-designed systematic reviews or meta-analyses of randomized controlled trials and RCTs**
Intermediate Quality	✓ Target population ✓ Sufficient sample size for the study design but could benefit from larger studies ✓ Control group identified ✓ Reasonably consistent results which limitations do not invalidate ✓ Fairly definitive conclusions ✓ **Low risk of bias** ✓ **Evidence primarily based on small randomized controlled trials; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; and/or well-designed observational studies**
Low Quality	✓ Insufficient sample size for the study design ✓ Discrepancies among reported data ✓ Errors in study design or analysis ✓ Missing significant information ✓ Unclear or inconsistent results ✓ **High risk of bias due to multiple flaws so that conclusions cannot be drawn High uncertainty about validity of conclusions**

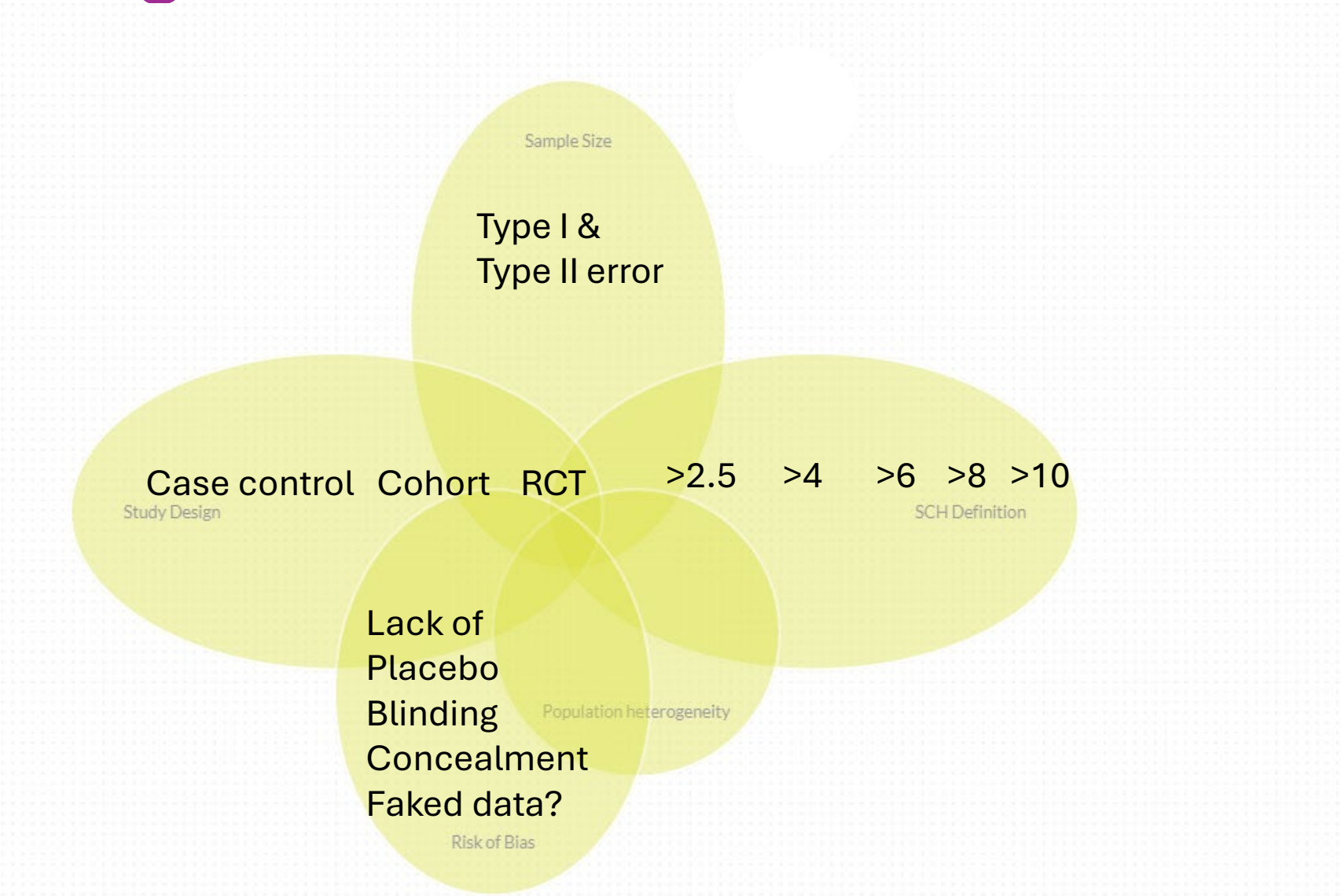
Strength of Evidence

Strength of Evidence	Definition
Grade A	High confidence in evidence **Larger or further study very unlikely to change reported effect** Majority of evidence supported by well-constructed RCTs or extremely strong and consistent observational studies
Grade B	Moderate confidence in evidence **Larger or further studies not likely to change reported effect but may more precisely identify magnitude of effect** Majority of evidence comprised of RCTs with potential weaknesses consistent observational studies with reasonably consistent
Grade C	Low confidence in evidence **Evidence lacking to support reported effect** Evidence comprised of observational studies with significant methodological flaws

Strength of Recommendation

Strength of Recommendation	Definition
Strong	Strong degree of confidence recommendation reflects best practice approach Recommendation based on **consistent evidence of high quality,** consideration that benefit of stated **recommendation outweighs potential risks**, and consensus of expert task force and Practice Committee review.
Moderate	Moderate degree of confidence recommendation reflects best practice approach Recommendation based on **limited evidence of high quality or mix of evidence** of high and intermediate quality or consistent body of mostly evidence of intermediate quality, consideration that benefit of stated recommendation outweighs potential risks, and consensus of expert task force and Practice Committee review.
Weak/Conditional	Low degree of confidence in stated recommendation **Low quality or insufficient evidence** to assess true measure of effect. Limited ability to assess benefit versus risk of intervention. Inability of expert task force or Practice Committee to reach evidence-based consensus.
No recommendation	Insufficient available evidence, lack of confidence or consensus to provide a recommendation for clinical practice.

Challenges in the Literature



Challenges in the Literature

- Data suggests 8-14% of RCTs are falsified
- ASRM formed Research Integrity Committee
  - 62 papers have allegations
  - 12 retractions
  - 6 expressions of concern
  - 3 erratum

FROM THE EDITOR-IN-CHIEF

Scientific integrity within *Fertility and Sterility* and formation of the Research Integrity Committee

Kurt T. Barnhart, M.D., M.S.C.E.
Editor-in-Chief, Fertility and Sterility
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https://doi.org/10.1016/j.fertnstert.2023.09.001

Important Perspectives

- In this updated version of the SCH guideline, the ASRM Practice Committee and assigned Task Force consciously decided to delve more deeply into the quality of the included studies

- Low risk / low cost of an intervention was not considered justification to recommend that intervention in the absence of evidence

Source Literature

- 498 papers identified and screened in literature search
- All papers reviewed by 2 members for inclusion
- Good shepherd adjudicated discrepancies
- 87 papers met inclusion criteria

Is SCH Associated with SAB?

Evidence

SCH and SAB

Clinical Endocrinology (2017) **86**, 816–824 doi: 10.1111/cen.13329

ORIGINAL ARTICLE

Preconception TSH and pregnancy outcomes: a population-based cohort study in 184 611 women

Shi Chen*, Xiang Zhou*, Huijuan Zhu*, Hongbo Yang*, Fengying Gong*, Linjie Wang*, Man Zhang†, Yu Jiang‡, Chengsheng Yan§, Jianqiang Li¶, Qing Wang**, Shikun Zhang†† and Hui Pan*

Table 3. Incidence of adverse pregnancy outcomes using different TSH cut-offs

	TSH (mIU/l)			TSH (mIU/l)		
Pregnancy outcomes	0·48–2·49 (N = 133 232) n (%)	2·50–10* (N = 51 379) n (%)	P†	0·48–4·28 (N = 177 471) n (%)	4·29–10* (N = 7140) n (%)	P†
Adverse events‡	37 502 (28·1)	15 217 (29·6)	<0·001	50 489 (28·4)	2230 (31·2)	0·001
Spontaneous abortion	3145 (2·4)	1442 (2·8)	<0·001	4320 (2·4)	267 (3·7)	<0·001

SCH and SAB

Subclinical Hypothyroidism and Thyroid Autoimmunity Are Not Associated With Fecundity, Pregnancy Loss, or Live Birth

Torie C. Plowden, Enrique F. Schisterman, Lindsey A. Sjaarda, Shvetha M. Zarek, Neil J. Perkins, Robert Silver, Noya Galai, Alan H. DeCherney, and Sunni L. Mumford

J Clin Endocrinol Metab, June 2016, 101(6):2358–2365

Table 3. Association Between TSH Level and Live Birth and Pregnancy Loss Among Women With Normal fT_4 (0.7–1.85 ng/dL), Within Women With One Prior Loss, Two Prior Losses, or Positive Antithyroid Antibody Status in the EAGeR Trial

	TSH ≥2.5 vs <2.5 mIU/L Among Pregnancies [b], RR (95% CI)		
Model	**One Previous Loss**	**Two Previous Losses**	**Positive Antithyroid Antibodies**
n	508	267	114
Live birth			
Unadjusted	0.96 (0.85–1.07)	1.00 (0.84–1.19)	1.03 (0.84–1.25)
Adjusted[a]	0.95 (0.85–1.06)	1.03 (0.86–1.24)	1.02 (0.84–1.25)
Any pregnancy loss			
Unadjusted	1.16 (0.82–1.63)	0.99 (0.63–1.56)	0.91 (0.46–1.81)
Adjusted	1.13 (0.80–1.59)	0.96 (0.61–1.52)	0.82 (0.41–1.65)
Clinical loss			
Unadjusted	1.33 (0.87–2.02)	1.18 (0.68–2.05)	1.10 (0.46–2.61)
Adjusted	1.32 (0.87–2.01)	1.18 (0.68–2.05)	1.03 (0.43–2.46)

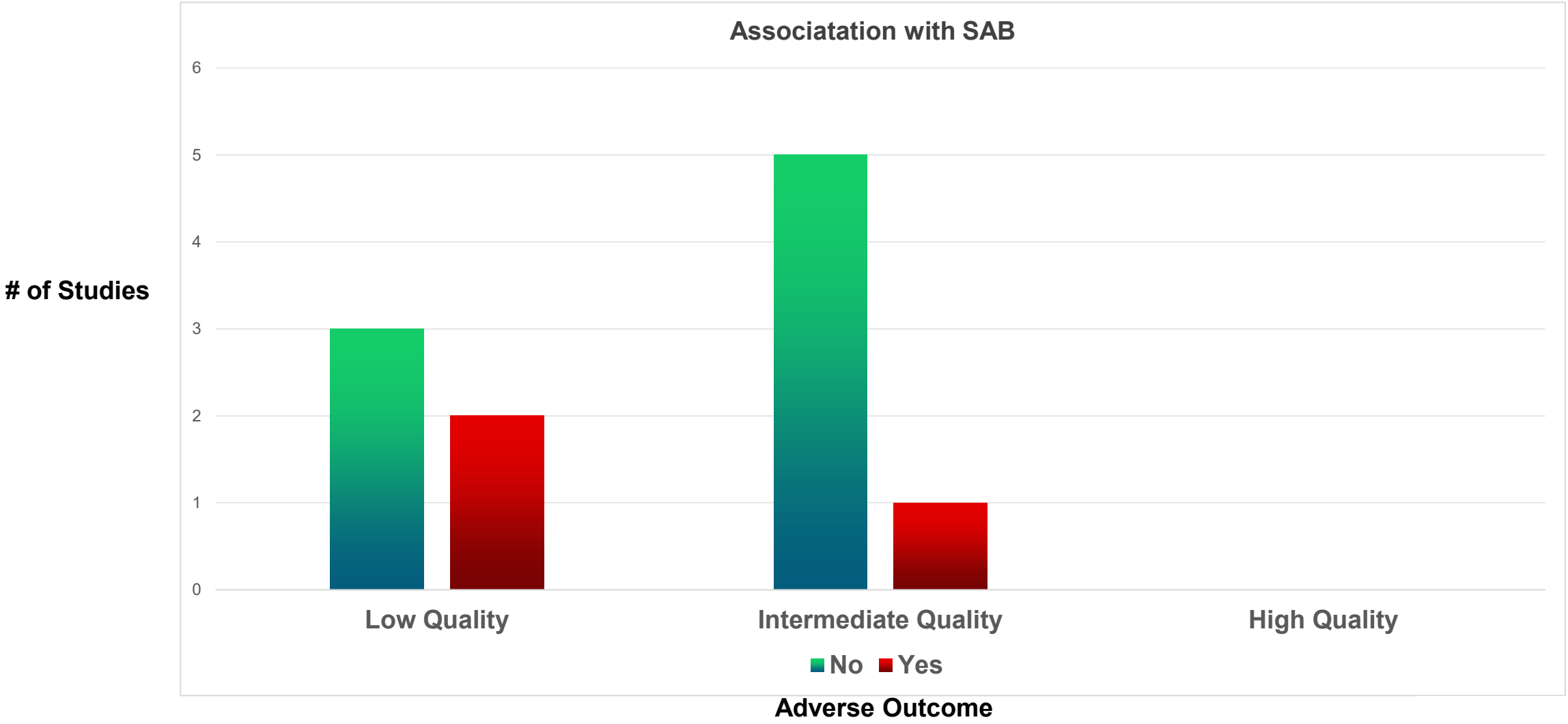
[a]Models adjusted for age and BMI.

[b]Models restricted to women who achieved an hCG pregnancy, with inverse probability weights used control for potential selection bias introduced by restricting to women who achieved pregnancy. Weights were based on factors associated with becoming pregnant, including age, parity, marital status, number of prior losses, and treatment assignment. Weighted log-binomial regression was used to estimate risk ratios and 95% CIs.

Study Quality and Outcome

	A	B	C	D	E	F	G	H	I	J
1			Quality	True SCH	>2.5 SCH					
2	New									
3	Zhao	metaanalysis	I	no	no					
4	Zhang	metaanalysis	I	no	yes					
5	van Dijk	prospec	L	no	-					
6	Uchida	prospec	I	no	-					
7	Plowden	RCT pro coh	I	-	no					
8	Marka	metaanalysis	I	-	yes					
9	Liu	prospec	I	yes	no					
10	Hernande	retro	L	-	yes					
11	Gingold	retro	I	-	no					
12	Coelho	retro	I	no	no					
13	Chen	retro	I	-	yes					
14	Chai	retro	L	no	-					
15	Cakmak	retro	L	yes	no					
16	Old									
17	Ashoor	retro	I	-	-	only used TSH as a linear predictor for all comers				
18	Benhadi	excluded		-	-					
19	De Vivo	retro	L	yes	-	only 8 women with SCH and unclear how defined				
20	Reh	retro	I	no	no					
21	Karakis	retro	L	-	no					
22	Tsunimi	retro	L	no						
23										
24			2/7 L	no = 8	no = 8	1/7 L				
25			2/3 L	yes = 3	yes = 4	1/4 L				
26										

Study Quality and Outcome



SCH and SAB

Summary Statement

- There is moderate evidence on the basis of intermediate- and low-quality studies with some contradictory findings that SCH during pregnancy is not associated with an increased risk of miscarriage. Most intermediate-quality studies do not show an increased risk. There is moderate evidence that TSH levels between 2.5 and 4.0 mIU/L are not associated with miscarriage.

Recommendations

- It is recommended to counsel women that SCH is not associated with an increased risk of miscarriage (strength of evidence: B; strength of recommendation: moderate).
- It is recommended to counsel women that a TSH levels between 2.5 and 4.0 mIU/L is not associated with an increased risk of miscarriage (strength of evidence: B; strength of recommendation: moderate).

Is SCH Associated with Infertility?

Evidence

SCH and Infertility

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2015, Article ID 132718, 6 pages
http://dx.doi.org/10.1155/2015/132718

Research Article

Impaired Fertility Associated with Subclinical Hypothyroidism and Thyroid Autoimmunity: The Danish General Suburban Population Study

Anne-Dorthe Feldthusen,[1,2] Palle L. Pedersen,[2,3] Jacob Larsen,[2,4] Tina Toft Kristensen,[2,5] Christina Ellervik,[6,7] and Jan Kvetny[2,8,9]

Table 1: Characteristics of women in The Danish General Suburban Population Study (GESUS).

	All	Mild (subclinical) hypothyroidism		
		No	yes	*P*-value
N (%)	11254 (100)	8770	758	
Age	56.3 (45.5–66.2)	55.4 (44.8–65.6)	55.6 (44.9–65.9)	0.43
Menopause, yes (%)	7129 (63.4)	5405 (61.6)	463 (61.1)	0.77
TSH, mU/L	1.8 (1.2–2.6)	1.7 (1.2–2.3)	4.6 (4.1–5.5)	<0.001
Total T3, nmol/L	1.6 (1.5–1.9)	1.7 (1.5–1.9)	1.6 (1.5–1.8)	0.38
Free T4, pmol/L	15 (14–17)	15 (14–17)	14 (13–15)	<0.001
TPOAb, U/mL	13 (20–32)	19 (12–27)	28 (15–699)	<0.001
Body mass index (BMI), kg/m^2	25.3 (22.6–28.8)	25.2 (22.5–28.7)	25.5 (22.8–29.2)	0.06
Smoker, yes (%)	1899 (16.9)	1527 (17.5)	66 (8.7)	<0.001
Prevalent hypothyroidism, yes (%)	922 (9.4)	NA	NA	
Prevalent hyperthyroidism, yes (%)	391 (4.2)	NA	NA	
Diabetes mellitus, yes (%)	576 (5.1)	392 (4.5)	40 (5.3)	0.31
Antihypertensive medication, yes (%)	2457 (21.8)	1816 (20.7)	140 (18.5)	0.14
Cholesterol lowering medication, yes (%)	1510 (8.5)	1096 (12.5)	91 (12.0)	0.69
Contraception, yes (%)	953 (8.5)	772 (8.8)	66 (8.7)	0.93
Income below EUR 60,000 €	4744 (43.7)	3588 (42.4)	292 (40.1)	0.25
Unemployment, yes (%)	6284 (55.8)	3690 (42.1)	318 (42.0)	0.95
Education, no (%)	1713 (15.2)	1291 (14.7)	95 (12.5)	0.57
Age at 1st child born	25 (22–28)	25 (22–28)	25 (22–29)	0.02
No children born, *N* (%)	1171 (10.5)	897 (10.3)	98 (13.0)	0.02
No pregnancies, *N* (%)	952 (8.5)	733 (8.4)	77 (10.2)	0.09
Spontaneous abortion, yes (%)	2261 (21)	1747 (20.8)	149 (20.6)	0.87

For continuous variables: median (interquartile range).
For SCH, *P* value: Chi-square for categorical comparisons and ranksum or Kruskal-Wallis test for continuous comparisons.

SCH and Infertility

Summary Statement

- There is weak evidence that SCH is not associated with an increased risk of infertility.

Recommendation

- There is insufficient evidence to counsel women that SCH is associated with infertility (strength of evidence: C; strength of recommendation: weak).

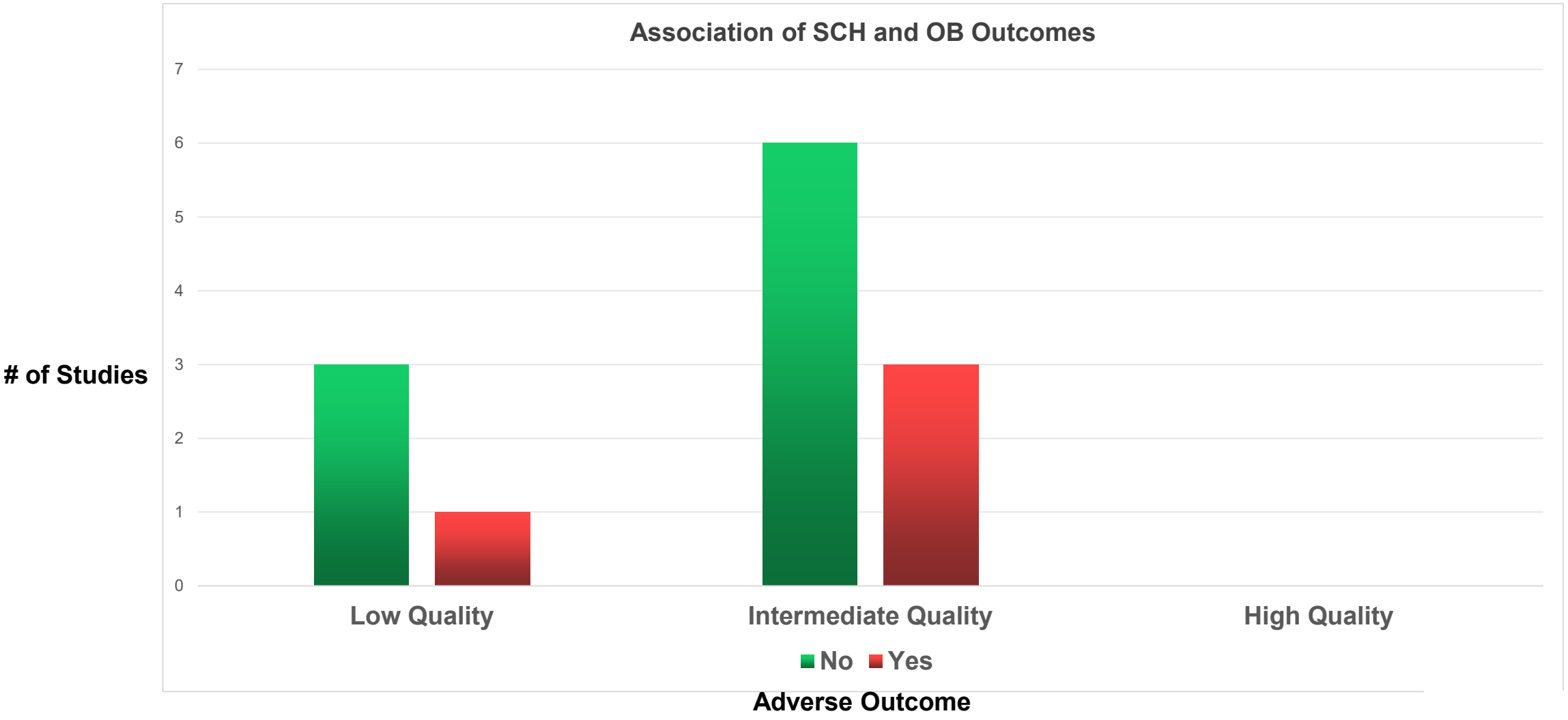
Is SCH Associated with Adverse OB Outcomes?

Evidence

SCH and OB Outcomes- Challenges

- Papers compared up to 35 OB Outcomes
- No corrections for multiple comparisons
- Studies with significant findings based on few cases
  - 2, 5 and 6 adverse outcomes in three studies
- No consistent findings in studies that did find statistical significance

Study Quality and Outcome



SCH and OB Outcomes

Summary Statement

- There is moderate-quality evidence that SCH during pregnancy is not associated with adverse obstetric outcomes. Although some studies show an increased risk, particularly with testing later in pregnancy, higher-quality studies with preconception and first-trimester testing predominately do not show an increased risk. There is insufficient evidence that TSH levels of 2.5–4 mIU/L are associated with adverse obstetric outcomes.

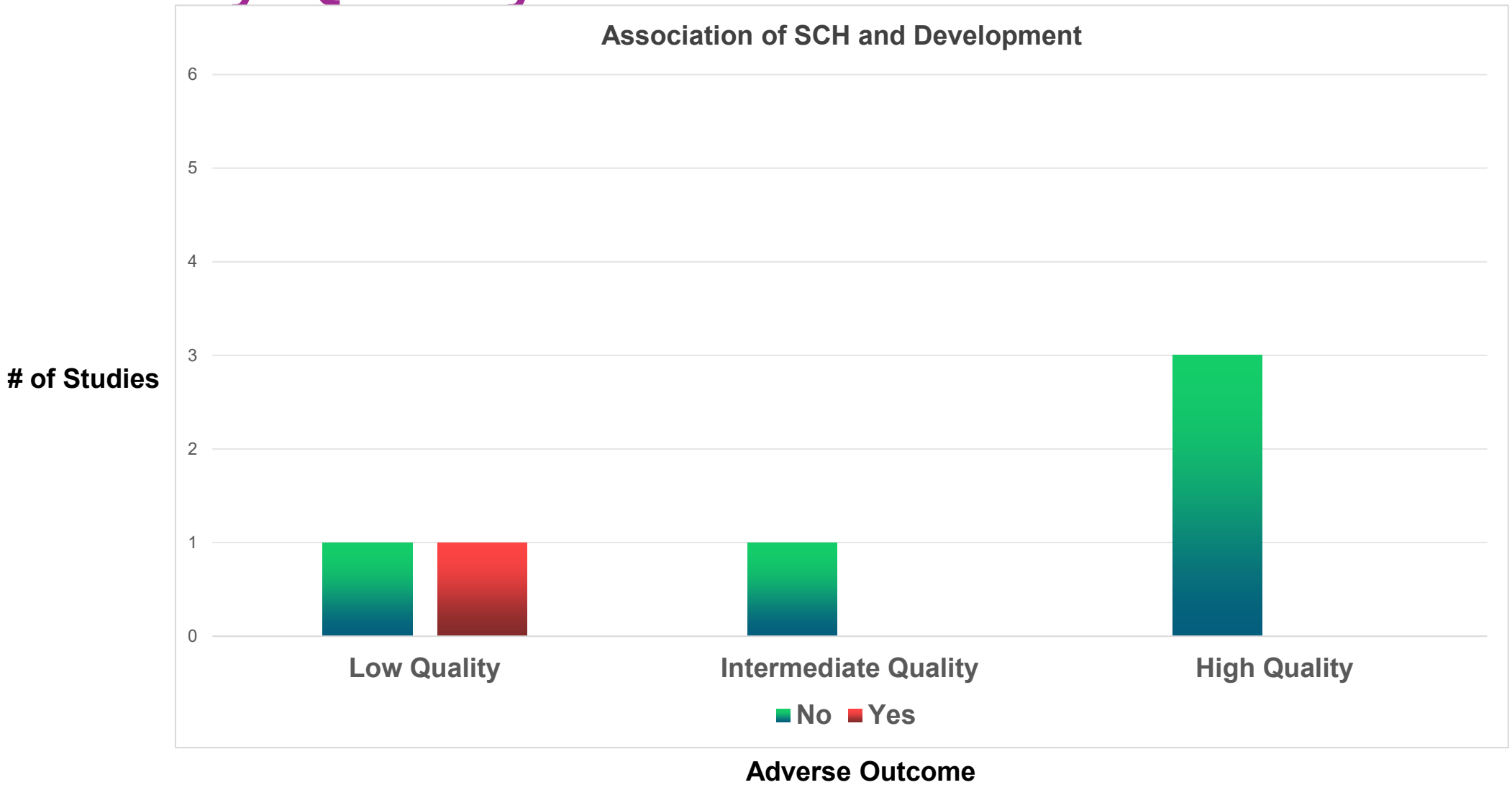
Recommendation

- It is recommended to counsel women that SCH is not associated with increased obstetric risk (strength of evidence B strength of recommendation: moderate).

Is SCH Associated with Developmental Outcomes?

Evidence

Study Quality and Outcome



SCH and Developmental Outcomes

Summary Statement

- There is strong evidence that SCH in pregnancy is not associated with adverse neurodevelopmental outcomes in offspring. There is insufficient evidence that pregnancy TSH levels between 2.5 and 4 mIU/L are associated with adverse developmental outcomes.

Conclusion

- It is recommended that women be counseled that SCH in pregnancy is not associated with adverse neurodevelopmental outcomes in offspring (strength of evidence: A; strength of recommendation: strong).

Does Treatment Improve Reproductive Outcomes?

Evidence

RCT #1

Study characteristics:

- Randomized trial
- 32 women per arm
- No randomization explanation
- No blinding
- No allocation concealment
- No placebo
- No sample size calculation
- Implantation primary outcome

Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection

Chung-Hoon Kim, M.D., Ph.D., Jun-Woo Ahn, M.D., Sunjung Park Kang, M.D., Sung-Hoon Kim, M.D., Hee-Dong Chae, M.D., and Byung-Moon Kang, M.D., Ph.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, South Korea

1650 Fertility and Sterility® Vol. 95, No. 5, April 2011 0015-0282/$36.00

doi:10.1016/j.fertnstert.2010.12.004

TABLE 2

Comparison of COS results and IVF/ICSI outcome.

Factor	LT4 treatment	Control	*P* value
No. of cycles initiated	32	32	
No. of cycles retrieved	32	32	
No. of ET cycles	32	32	
Cycles with ICSI, n (%)	14 (43.8)	14 (43.8)	NS[a]
Days of rhFSH	9.1 ± 1.2	9.0 ± 1.1	NS[b]
Total dose of rhFSH	1,880.6 ± 425.5	1,919.9 ± 397.7	NS[b]
Days of GnRH antagonist	4.3 ± 1.0	4.3 ± 1.0	NS[b]
On the day of hCG injection			
TSH (mIU/L)	2.9 ± 1.0	6.8 ± 1.9	<.001[a]
FT4 (ng/dL)	1.3 ± 0.1	1.2 ± 0.2	.017[a]
PRL (ng/mL)	15.8 ± 3.3	16.3 ± 3.5	NS[b]
No. of follicles ≥14 mm	8.9 ± 3.4	9.1 ± 3.3	NS[b]
EMT (mm)	10.1 ± 1.1	9.8 ± 1.2	NS[b]
On the day of β-hCG measurement			
TSH (mIU/L)	2.3 ± 0.4	6.9 ± 2.0	<.001[a]
FT4 (ng/dL)	1.4 ± 0.3	1.0 ± 0.2	<.001[a]
No. of oocytes retrieved	9.3 ± 3.9	9.2 ± 3.2	NS[b]
No. of mature oocytes	8.2 ± 3.4	7.5 ± 2.6	NS[b]
No. of fertilized oocytes	8.1 ± 3.4	7.2 ± 2.3	NS[b]
No. of grade I, II embryos	3.3 ± 1.6	2.2 ± 1.3	.007[b]
No. of embryos transferred	2.9 ± 0.5	2.9 ± 0.4	NS[b]
No. of embryos cryopreserved	2.5 ± 2.7	1.8 ± 2.3	NS[b]
Embryo implantation rate, % (n)	26.9 (25/93)	14.9 (14/94)	.044[a]
Clinical PR per cycle initiated, % (n)	53.1 (17/32)	37.5 (12/32)	NS[a]
Miscarriage rate, % (n)	0 (0/17)	33.3 (4/12)	.021[a]
Live birth rate per cycle initiated, % (n)	53.1 (17/32)	25.0 (8/32)	.039[a]

Note: Values are mean ± SD unless otherwise noted. PR = pregnancy rate; NS = not significant.

[a] Fisher's exact test or χ^2 test.

[b] Student's *t* test.

Kim. LT4 for subclinical hypothyroidism. Fertil Steril 2011.

P=0.33

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[b] Student's *t* test.

Kim. LT4 for subclinical hypothyroidism. Fertil Steril 2011.

Unit of analysis???

P=0.11

What is Type 1 error?

- False positive
- Occurs when a researcher rejects a null hypothesis that is actually true
- This means that the researcher concludes that there is a significant difference or effect when there is not
- Is type 1 error more likely in large or small studies?
- Risk **does not change** based on study size (set at 5% by convention)
- This is different than concerns that a large study finds statistically significant findings that are not clinically meaningful
- BUT- is more sensitive to a single outcome change in small studies
- Thus readers should be more concerned of false positives in small studies

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[a] Fisher's exact test or χ^2 test.

[b] Student's *t* test.

Kim. LT4 for subclinical hypothyroidism. Fertil Steril 2011.

P=0.08-0.18

RCT #2

Study characteristics:

- Randomized trial
- 35 women per arm
- Physician not blinded
- No placebo

Original Article

IMPROVED IN VITRO FERTILIZATION OUTCOMES AFTER TREATMENT OF SUBCLINICAL HYPOTHYROIDISM IN INFERTILE WOMEN

Ashraf Hany Abdel Rahman, MD[1]; Hadeer Aly Abbassy, MD[2]; Aly Abd Elatif Abbassy, MD, FACE[3]

792 ENDOCRINE PRACTICE Vol 16 No. 5 September/October 2010

Table 2
Characteristics of 70 Women With Subclinical Hypothyroidism 1 Month into the Study

Characteristics	Group A (levothyroxine treatment) (n = 35)	Group B (placebo) (n = 35)	*P* value
Basal FSH, mean (SD), mIU/mL[a]	7.6 (2.2) (range, 3.2-12)	6.3 (2) (range, 2.3-10.3)	.285
Basal LH, mean (SD), mIU/mL[b]	7.4 (1.9) (range, 3.6-11.2)	8.3 (1.6) (range, 5.1-11.5)	.129
Basal prolactin, mean (SD), ng/mL[c]	21.4 (1.5) (range, 19.9-25.9)	24.2 (2) (range, 22.2-30.2)	.546
Basal thyrotropin, mean (SD), mIU/L[d]	1.1 (0.3) (range, 0.8-2)	4.9 (0.7) (range, 4.2-7)	.026
Basal free T_3, mean (SD), pg/mL[e]	3.1 (0.7) (range, 1.68-4.5)	3 (0.7) (range, 1.49-4.6)	.109
Basal free T_4, mean (SD), ng/dL[f]	0.95 (0.4) (range, 0.5-2.2)	1.01 (0.5) (range, 0.5-2.5)	.140
No. stimulation days, mean (SD)	12.8 (2) (range, 10.8-18.8)	13.4 (1.7) (range, 11.7-18.5)	.517
Estradiol at aspiration, mean (SD), pg/mL	1750 (155) (range, 1440-2060)	1069 (56) (range, 957-1181)	.012
No. follicles punctured, mean (SD)	15.6 (1.3) (range, 13-18.2)	10 (2.2) (range, 5.6-14.4)	.029
No. oocytes retrieved, mean (SD)	6.2 (0.7) (range, 5.5-8.3)	6.1 (0.9) (range, 5.2-8.8)	.450
No. of metaphase II at time of injection	29	14	.019
Miscarriage, %	9	13	.031
Fertilization, %	51.9	18.8	.015
Pregnancy, %	35	10	.021
Delivery, %	26	3	.017

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; T_3, triiodothyronine; T_4, thyroxine.
[a] Reference range, 3.5-12.5 mIU/mL.
[b] Reference range, 2.4-12.6 mIU/mL.
[c] Reference range, 4.79-23.3 ng/mL.
[d] Reference range, 0.27-4.2 mIU/L.
[e] Reference range, 2.56-4.4 pg/mL.
[f] Reference range, 0.9-2.59 ng/dL.

Original Article

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792 ENDOCRINE PRACTICE Vol 16 No. 5 September/October 2010

CORRECTION

It was brought to our attention that the data in the manuscript, "Improved In Vitro Fertilization Outcomes After Treatment of Subclinical Hypothyroidism in Infertile Women," by Rahman et al (*Endocr Pract*. 2010;16:792-797) had statistical errors, as well as errors in Table 2. Rather than percentage rates for miscarriage and pregnancy, the percentages should have been absolute numbers. In recalculating the values, levothyroxine therapy of subclinical hypothyroidism did not affect the miscarriage rate ($P = .44$), but did affect the pregnancy rate with a more significant P value of .0001. Our calculations are shown below.

Lewis Braverman, MD, FACP, FACE
Editor-in-Chief
Endocrine Practice

For the outcome of pregnancy:
2 × 2 contingency table

	Outcome 1	Outcome 2	Total
Group 1	35	0	**35**
Group 2	10	25	**35**
Total	**45**	**25**	**70**

Fisher exact test
The 2-tailed P value <.0001

For the outcome of miscarriage:
2 × 2 contingency table

	Outcome 1	Outcome 2	Total
Group 1	9	26	**35**
Group 2	13	22	**35**
Total	**22**	**48**	**70**

Fisher exact test
The 2-tailed P value = .4403

Braverman, Endocrine Practice 2011;17:526

For the outcome of pregnancy:
2 × 2 contingency table

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Basal FSH, mean (SD), mIU/mL[a]	7.6 (2.2) (range, 3.2-12)	6.3 (2) (range, 2.3-10.3)	.285
Basal LH, mean (SD), mIU/mL[b]	7.4 (1.9) (range, 3.6-11.2)	8.3 (1.6) (range, 5.1-11.5)	.129
Basal prolactin, mean (SD), ng/mL[c]	21.4 (1.5) (range, 19.9-25.9)	24.2 (2) (range, 22.2-30.2)	.546
Basal thyrotropin, mean (SD), mIU/L[d]	1.1 (0.3) (range, 0.8-2)	4.9 (0.7) (range, 4.2-7)	.026
Basal free T_3, mean (SD), pg/mL[e]	3.1 (0.7) (range, 1.68-4.5)	3 (0.7) (range, 1.49-4.6)	.109
Basal free T_4, mean (SD), ng/dL[f]	0.95 (0.4) (range, 0.5-2.2)	1.01 (0.5) (range, 0.5-2.5)	.140
No. stimulation days, mean (SD)	12.8 (2) (range, 10.8-18.8)	13.4 (1.7) (range, 11.7-18.5)	.517
Estradiol at aspiration, mean (SD), pg/mL	1750 (155) (range, 1440-2060)	1069 (56) (range, 957-1181)	.012
No. follicles punctured, mean (SD)	15.6 (1.3) (range, 13-18.2)	10 (2.2) (range, 5.6-14.4)	.029
No. oocytes retrieved, mean (SD)	6.2 (0.7) (range, 5.5-8.3)	6.1 (0.9) (range, 5.2-8.8)	.450
No. of metaphase II at time of injection	29	14	.019
Miscarriage, %	9	13	.031
Fertilization, %	51.9	18.8	.015
Pregnancy, %	35	10	.021
Delivery, %	26	3	.017

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; T_3, triiodothyronine; T_4, thyroxine.
[a] Reference range, 3.5-12.5 mIU/mL.
[b] Reference range, 2.4-12.6 mIU/mL.
[c] Reference range, 4.79-23.3 ng/mL.
[d] Reference range, 0.27-4.2 mIU/L.
[e] Reference range, 2.56-4.4 pg/mL.
[f] Reference range, 0.9-2.59 ng/dL.

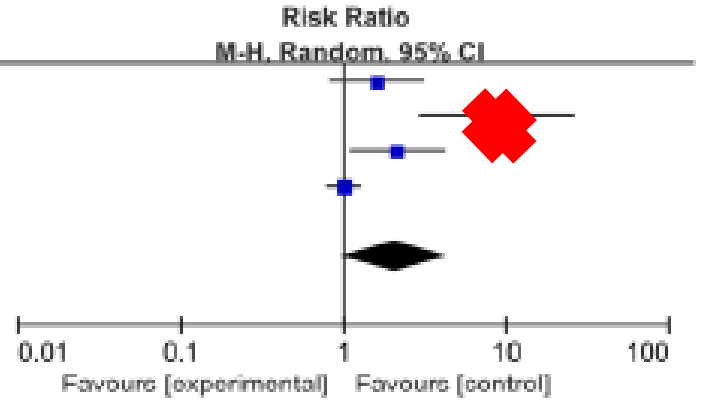
Meta-analysis

B

Study or Subgroup	LT4 supplementation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Negro 2005	16	43	10	43	25.3%	1.60 [0.82, 3.12]	2005
Abdel Rahman 2010	26	35	3	35	18.9%	8.67 [2.89, 26.02]	2010
Kim 2011	17	32	8	32	25.1%	2.13 [1.07, 4.21]	2011
Wang 2017	90	282	91	285	30.6%	1.00 [0.79, 1.27]	2017
Total (95% CI)		**392**		**395**	**100.0%**	**2.05 [0.96, 4.36]**	
Total events	149		112				

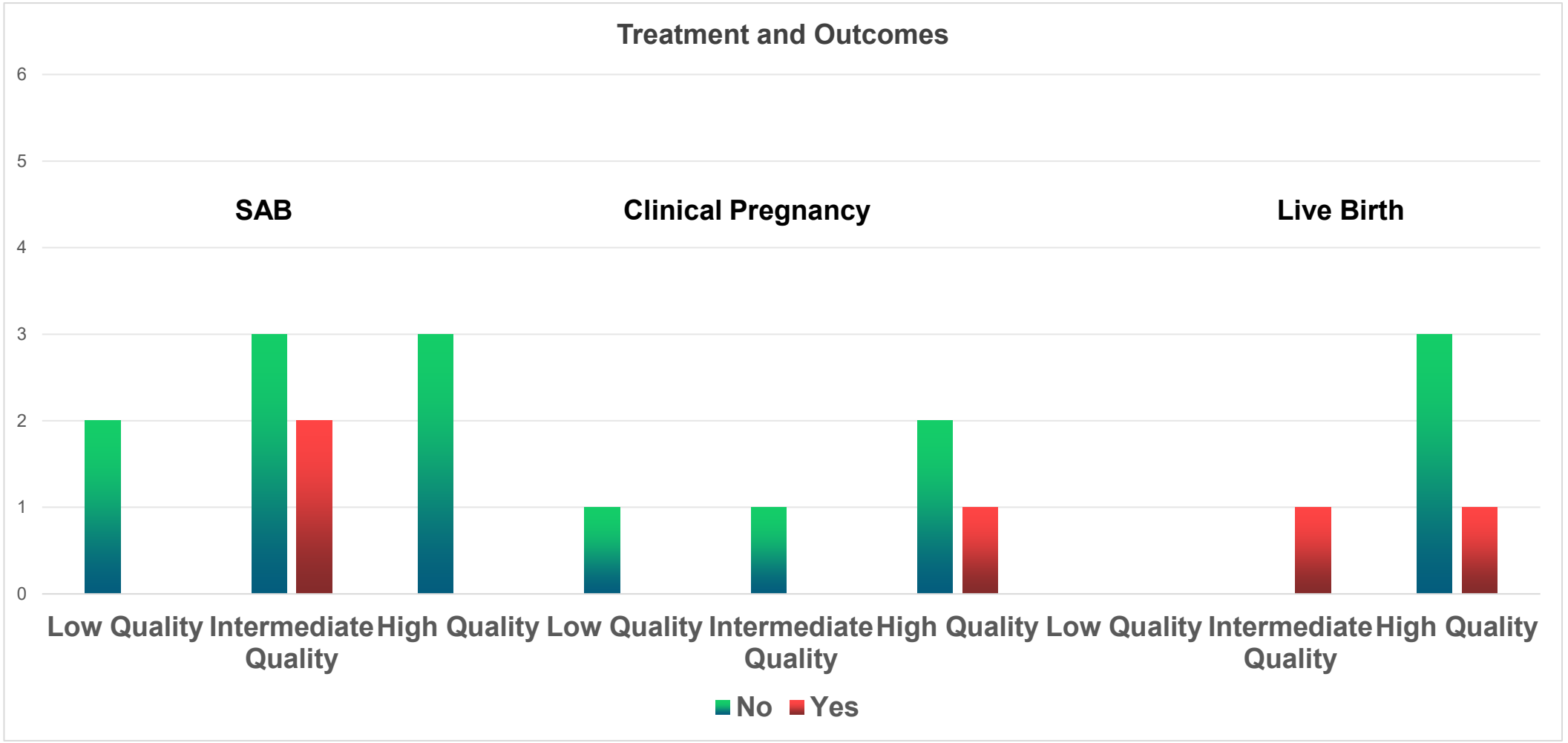
Heterogeneity: $Tau^2 = 0.47$; $Chi^2 = 18.82$, df = 3 (P = 0.0003); $I^2 = 84\%$

Test for overall effect: Z = 1.86 (P = 0.06)



Rao et al. Reproductive Biology and Endocrinology (2018) 16:92

Study Quality and Outcome



SCH Treatment and Reproductive Outcomes

Summary Statements

- There is moderate evidence that treatment of SCH with levothyroxine does not improve pregnancy loss, clinical pregnancy, or LB.

Recommendation

- It is not recommended to treat pregnant women or women desiring pregnancy who have a diagnosis of SCH with levothyroxine, as treatments have not been demonstrated to reduce pregnancy loss nor to improve clinical pregnancy or LB outcomes (strength of evidence B; strength of recommendation: moderate).
- Thyroid-stimulating hormone and T4 levels should be tested in patients with signs or symptoms of hypothyroidism (including irregular menstrual cycles) rather than in all patients with infertility (strength of evidence: B; strength of recommendation: moderate).

Does Treatment Improve Developmental Outcomes?

Evidence

SCH Treatment and Developmental Outcomes

Study characteristics:

- Randomized trial
- 400 women per arm
- Randomized to screening/Rx

  Versus control
- Screened/Rx at 12 weeks
- Children evaluated @ 3 years


The NEW ENGLAND JOURNAL of MEDICINE

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Antenatal Thyroid Screening and Childhood Cognitive Function

John H. Lazarus, M.D., Jonathan P. Bestwick, M.Sc., Sue Channon, D.Clin.Psych., Ruth Paradice, Ph.D., Aldo Maina, M.D., Rhian Rees, M.Sc., Elisabetta Chiusano, M.Psy., Rhys John, Ph.D., Varvara Guaraldo, M.S.Chem., Lynne M. George, H.N.C., Marco Perona, M.S.Chem., Daniela Dall'Amico, M.D., Arthur B. Parkes, Ph.D., Mohammed Joomun, M.Sc., and Nicholas J. Wald, F.R.S.

SCH Treatment and Developmental Outcomes

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Table 2. Standardized Full-Scale Child IQ and Scores on the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function, Preschool Version (Brief-P), According to Study Group.*

Test	Screening Group (N=390)	Control Group (N=404)	Difference (95% CI) (Control Group – Screening Group)†	P Value
IQ				
Mean	99.2±13.3	100.0±13.3	0.8 (–1.1 to 2.6)	0.40
<85 (% of children)	12.1	14.1	2.1 (–2.6 to 6.7)	0.39
CBCL T score‡				
Mean	44.4±12.4	45.1±13.6	0.7 (–1.2 to 2.5)	0.49
Brief-P T score§				
Median	40	40	0	0.59
Interquartile range	47–55	47–55		

* Plus–minus values are means ±SD. The full-scale child IQ test was standardized so that for each psychologist, the mean score among the children in the control group whom they tested was 100. In the screening group, the women were assigned to treatment with levothyroxine.
† For percentages of children with an IQ below 85, the absolute (percentage-point) differences are shown.
‡ For the CBCL, a T score above the 98th percentile is indicative of a clinically significant problem.
§ For the Brief-P, a T score above 65 is indicative of a clinically significant problem.

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SCH Treatment and Developmental Outcomes

Study characteristics:

- Follow up of CATS I
- Randomized trial
- 400 women per arm
- Randomized to screening/Rx

  Versus control
- Screened/Rx at 12 weeks
- Children evaluated @ 9 years

Controlled Antenatal Thyroid Screening II: Effect of Treating Maternal Suboptimal Thyroid Function on Child Cognition

Charlotte Hales,[1] Peter N. Taylor,[1] Sue Channon,[2] Ruth Paradice,[3] Kirsten McEwan,[2] Lei Zhang,[1] Michael Gyedu,[1] Ameen Bakhsh,[1] Onyebuchi Okosieme,[1] Ilaria Muller,[1] Mohd S. Draman,[1] John W. Gregory,[1] Colin Dayan,[1] John H. Lazarus,[1] D. Aled Rees,[4] and Marian Ludgate[1]

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SCH Treatment and Developmental Outcomes

Study characteristics:

- Randomized trial
- 400 women per arm
- Randomized to screening/Rx

  Versus control
- Screened/Rx at 12 weeks

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SCH Treatment and Developmental Outcomes

Table 2. Logistic Regressions for Odds of IQ Below 85

IQs	Models	Merged SGTF to Normal-GTF OR (95% CI)	*P* Interaction	OR Untreated (95% CI)	OR Treatment (95% CI)	*P* Treatment Interaction
FSIQ	1	1.58 (0.78, 3.21)	0.206	1.97 (0.86, 4.50)	0.65 (0.26, 1.63)	0.355
	2	1.57 (0.77, 3.19)	0.217	1.98 (0.86, 4.55)	0.63 (0.25, 1.59)	0.325
	3	1.38 (0.66, 2.86)	0.389	1.77 (0.75, 4.16)	0.61 (0.23, 1.58)	0.308
	4	1.15 (0.52, 2.51)	0.731	1.33 (0.53, 3.34)	0.75 (0.27, 2.06)	0.576
VCIQ	1	1.08 (0.57, 2.03)	0.820	0.89 (0.38, 2.09)	1.38 (0.55, 3.48)	0.491
	2	1.07 (0.57, 2.02)	0.833	0.89 (0.38, 2.09)	1.36 (0.54, 3.44)	0.506
	3	0.99 (0.52, 1.88)	0.968	0.82 (0.34, 1.93)	1.38 (0.54, 3.53)	0.491
	4	0.93 (0.47, 1.83)	0.834	0.70 (0.29, 1.73)	1.62 (0.62, 4.20)	0.317
PRIQ	1	1.82 (0.84, 3.94)	0.130	2.54 (1.06, 6.07)	0.49 (0.18, 1.33)	0.156
	2	1.82 (0.84, 3.94)	0.131	2.54 (1.06, 6.07)	0.49 (0.18, 1.33)	0.156
	3	1.60 (0.73, 3.53)	0.238	2.31 (0.95, 5.62)	0.46 (0.17, 1.28)	0.132
	4	1.35 (0.59, 3.09)	0.482	1.78 (0.69, 4.56)	0.56 (0.19, 1.58)	0.268
WMIQ	1	1.48 (0.78, 2.81)	0.232	1.35 (0.60, 3.04)	1.17 (0.50, 2.77)	0.715
	2	1.47 (0.77, 2.79)	0.241	1.35 (0.60, 3.05)	1.15 (0.49, 2.73)	0.742
	3	1.33 (0.69, 2.57)	0.393	1.21 (0.53, 2.78)	1.18 (0.49, 2.84)	0.713
	4	1.26 (0.63, 2.53)	0.513	1.04 (0.43, 2.50)	1.42 (0.57, 3.52)	0.449
PSIQ	1	0.79 (0.36, 1.71)	0.550	0.88 (0.33, 2.32)	0.81 (0.25, 2.61)	0.729
	2	0.78 (0.36, 1.69)	0.524	0.88 (0.33, 2.33)	0.79 (0.24, 2.53)	0.688
	3	0.75 (0.34, 1.63)	0.463	0.85 (0.32, 2.27)	0.77 (0.24, 2.49)	0.664
	4	0.75 (0.33, 1.68)	0.482	0.82 (0.20, 2.24)	0.85 (0.26, 2.77)	0.783

Data are expressed as OR, with 95% CIs. Model 1, unadjusted; model 2, adjusted for child's sex; model 3, adjusted for model 2 and whether the mother breastfed >1 month and mother's age at time of study consent during pregnancy; model 4, adjusted for model 3 and where the child was assessed, child's language spoken at school and home, and social deprivation score.

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SCH Treatment and Developmental Outcomes

Study characteristics:

- Randomized trial
- 300 women per arm
- Randomized to screening/Rx
  Versus control
- Screened/Rx at 16 weeks
- Children evaluated @ 5 years


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 2, 2017 VOL. 376 NO. 9

Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy

B.M. Casey, E.A. Thom, A.M. Peaceman, M.W. Varner, Y. Sorokin, D.G. Hirtz, U.M. Reddy, R.J. Wapner, J.M. Thorp, Jr., G. Saade, A.T.N. Tita, D.J. Rouse, B. Sibai, J.D. Iams, B.M. Mercer, J. Tolosa, S.N. Caritis, and J.P. VanDorsten, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

SCH Treatment and Developmental Outcomes

Table 2. Pregnancy and Neonatal Outcomes.*

Outcome	Subclinical Hypothyroidism			Hypothyroxinemia		
	Levothyroxine (N=339)	Placebo (N=338)	P Value	Levothyroxine (N=263)	Placebo (N=261)	P Value
Maternal						
Week of gestation at delivery	39.1±2.5	38.9±3.1	0.57	39.0±2.4	38.8±3.1	0.46
Preterm birth — no. (%)						
At <34 wk	9 (3)	10 (3)	0.81	10 (4)	7 (3)	0.47
At <37 wk	31 (9)	37 (11)	0.44	31 (12)	20 (8)	0.11
Placental abruption — no. (%)	1 (<1)	5 (1)	0.12	3 (1)	2 (1)	1.00
Gestational hypertension — no. (%)	33 (10)	36 (11)	0.69	20 (8)	24 (9)	0.51
Preeclampsia — no. (%)	22 (6)	20 (6)	0.76	9 (3)	11 (4)	0.64
Gestational diabetes — no. (%)	25 (7)	22 (7)	0.66	21 (8)	24 (9)	0.62
Fetal or neonatal†						
Stillbirth or miscarriage — no. (%)	4 (1)	7 (2)	0.36	2 (1)	5 (2)	0.28
Neonatal death — no. (%)	0	1 (<1)	0.50	1 (<1)	1 (<1)	1.00
Apgar score at 1 min <4 — no. (%)	6 (2)	7 (2)	0.76	6 (2)	7 (3)	0.76
Apgar score at 5 min <7 — no. (%)	2 (1)	3 (1)	0.69	2 (1)	4 (2)	0.45
Admission to NICU — no. (%)	29 (9)	21 (6)	0.24	31 (12)	31 (12)	0.97
Birth weight <10th percentile — no. (%)	33 (10)	27 (8)	0.45	23 (9)	20 (8)	0.68
Head circumference — cm	33.9±1.8	33.9±1.7	0.46	33.9±1.8	34.2±1.6	0.19
Respiratory distress syndrome — no. (%)	9 (3)	6 (2)	0.45	4 (2)	5 (2)	0.75
Retinopathy of prematurity — no. (%)	1 (<1)	0	1.00	0	0	—
Necrotizing enterocolitis — no. (%)	1 (<1)	1 (<1)	1.00	2 (1)	0	0.50
Bronchopulmonary dysplasia — no. (%)	0	1 (<1)	0.50	0	1 (<1)	0.49
Composite neonatal outcome — no. (%)‡	7 (2)	12 (4)	0.24	5 (2)	7 (3)	0.55
Respiratory therapy ≥1 day — no. (%)	11 (3)	11 (3)	0.99	13 (5)	12 (5)	0.85
No. of days in hospital nursery			0.43			0.39
Median	2	2		2	2	
95% CI	2–2	2–2		2–2	2–2	

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SCH Treatment and Developmental Outcomes

Table 3. Developmental and Behavioral Outcomes in Offspring of Mothers with Subclinical Hypothyroidism.*

Outcome	Levothyroxine		Placebo		Difference (95% CI)†	P Value
	No. of Children	Median Value (95% CI)	No. of Children	Median Value (95% CI)		
Primary outcome‡	323	97 (94 to 99)	326	94 (92 to 96)	0 (–3 to 2)	0.71
Bayley-III score§						
At 12 mo						
Cognitive	311	100 (95 to 100)	315	100 (95 to 100)	0 (0 to 0)	0.63
Motor	312	97 (97 to 97)	314	97 (97 to 97)	0 (0 to 3)	0.83
Language	309	94 (94 to 97)	312	94 (94 to 97)	0 (0 to 3)	0.48
At 24 mo						
Cognitive	308	90 (90 to 90)	302	90 (90 to 90)	0 (0 to 0)	0.59
Motor	304	97 (97 to 97)	300	97 (97 to 100)	0 (0 to 3)	0.31
Language	300	89 (89 to 91)	296	91 (89 to 94)	0 (0 to 3)	0.30
Differential Ability Scales–II scores						
Overall at 36 mo	304	90 (88 to 93)	308	90 (87 to 93)	0 (–2 to 3)	0.90
Recall of digits forward at 48 mo	298	84 (76 to 91)	299	84 (76 to 91)	0 (–5 to 7)	0.60
Recognition of pictures at 48 mo	298	74 (74 to 80)	302	74 (74 to 80)	0 (–6 to 0)	0.52
Child Behavior Checklist T score¶						
At 36 mo	306	46 (45 to 48)	309	46 (45 to 48)	0 (–2 to 2)	0.99
At 60 mo	314	44 (43 to 46)	313	44 (42 to 46)	0 (–2 to 2)	0.96
Conners' Rating Scales–Revised ADHD score at 48 mo‖	302	48 (47 to 49)	303	49 (47 to 51)	0 (–1 to 2)	0.37
WPPSI-III at 60 mo	311	97 (95 to 99)	314	95 (93 to 97)	0 (–3 to 2)	0.89

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SCH Treatment and Developmental Outcomes

Summary Statement

- There is strong evidence, on the basis of three randomized clinical trials, that levothyroxine therapy for women with SCH diagnosed in pregnancy has no benefit for obstetrical, neonatal, childhood IQ, or neurodevelopmental outcomes.

Recommendation

- Levothyroxine therapy for SCH diagnosed in pregnancy is not recommended for the indication of improving developmental outcomes (strength of evidence: A; strength of recommendation: strong).

SCH Treatment and Harm???

- Heat intolerance
- Sweats
- Chills
- Heart palpitations
- Arrythmias
- Diarrhea
- Weight change
- Hair thinning
- Tremors
- Mood changes
- Sleep disturbances
- Fatigue
- Anxiety
- Bone loss

Extra blood draws
Unnecessary medicine
Delayed care

ACOG
The American College of Obstetricians and Gynecologists

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 223 *(Replaces Practice Bulletin Number 148, April 2015)*

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the Committee on Practice Bulletins—Obstetrics with the assistance of Brian M. Casey, MD and Torri D. Metz, MD, MS in collaboration with American Academy of Family Physicians liaison Jeff Quinlan, MD.

Thyroid Disease in Pregnancy

(17, 36, 44). Currently, there is no evidence that identification and treatment of subclinical hypothyroidism during pregnancy improves these outcomes (40–42, 45).

Other Society Guidance

Question	Comparison of other recommendations; differences highlighted in yellow & similarities in green						
	ASRM 2021 prooposed	**ASRM 2015**	**ACOG 2015**	**ATA**	**ETA**	**Cochrane**	**Endocrine**
Is untreated SCH associated with miscarriage	No	Yes					
	Intermediate	Fair					
	Don't counsel on a proven association	N/A					
Is untreated SCH associated with infertility	Insufficient	Insufficient					
	Low	N/A					
	Don't counsel on a proven association	N/A					
Is SCH associated with adverse OB outcomes	No	Yes					
	Intermediate	Fair					
	Don't countsel on a proven association	N/A					
Is untreated SCH associated with developmental c	No	Yes	No				
	Good	Fair	N/A				
	Counsel on no association	N/A	N/A				
Does SCH treatment improve pregnancy outcomes?	No	Yes	No	No	Yes	No	No
	Good to Fair	Good	N/A	Insufficient	Treat over TSH of 4	Lack of RCT eviden	Yet recommended because "potential ben
	Do not treat SCH for pregnancy outcomes	N/A	N/A		based entirely on Velkenier SR/MA which is based on retracted Rahman study		
Does treatment of SCH improve developmental ou	No	Yes	No				No
	High- 3 new RCTs	Fair (one RCT)	N/A				Yet recommended because "potential ben
	Do not treat SCH for development outcome:	N/A	N/A				
Are thyroid Abs associated with adverse outcomes	conflicting	Yes		Unclear	Yes		
	Low to insufficient	Good		N/A	Treat if TPO + TSH >4		
	Universal screening not recommended	Treat over 2.5 with + Abs	Universal screening not recommended		They say no evidence of treatment benefit, yet recommend it		
	Targetted screening can be considered		Targetted screening can be considered	Insufficient evidence for Tx'			

Conclusion

- **Screen for thyroid disease on a case finding basis**
  - Clinical suspicion
  - Personal or family history of thyroid disease
  - Diabetes
- **Screen with TSH and FT4**
- **Treat overt hypothyroidism / do not treat SCH**
- **Counsel women with SCH for long-term risks**

Clinical Conundrum

Slow Adopters

Fast Adopters

Failure to implement helpful interventions

Too slow to adopt interventions
Awaiting strong level I evidence

Too fast to adopt interventions
Acting without level I evidence

Implement un-helpful or harmful interventions

Clinical Conundrum

Slow Adopters ← Fast Adopters

Failure to implement helpful interventions

Too slow to adopt interventions
Awaiting strong level I evidence

Too fast to adopt interventions
Acting without level I evidence

Implement un-helpful or harmful interventions

Thank You!

NIH REI Fellows 2023-2024