

Is Assisted Conception Affecting Neonatal Thyroid Function? Insights From a Case-Control Study

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INTRODUCTION

Assisted reproductive technologies (ART) often involve substantial maternal hormonal manipulation, especially through **controlled ovarian stimulation (COS)**. Although COS primarily targets the **hypothalamic–pituitary–gonadal axis**, emerging evidence suggests it may also affect the **hypothalamic–pituitary–thyroid axis**. These endocrine shifts may influence the fetus, especially during **early fetal thyroid development**, when fetal function is heavily reliant on maternal hormone supply.

OBJECTIVES

• PRIMARY AIM

To assess whether the **mode of conception** -spontaneous vs. ART- is associated with **elevated neonatal TSH levels**

• SECONDARY AIMS

To explore whether **specific ART-related factors**, **maternal thyroid function**, **maternal thyroid autoimmunity**, **mode of delivery**, and **neonatal feeding method**, may influence **neonatal thyroid function**

STUDY DESIGN AND METHODS

Design: Retrospective, observational, matched case-control study

Setting: Vittore Buzzi Children’s Hospital, Milan, Italy

Study period: June 1st 2022 - August 31st 2024

Participants: Term singleton newborns who underwent TSH screening at 48–72 hours of life

Exclusion criteria: Pre or post-term birth, small or large for gestational age, multiple pregnancies, major maternal complications, NICU admission, or incomplete records

Group definition:

- CASES:** Neonatal TSH ≥ 6 μ U/mL
- CONTROLS:** Neonatal TSH < 6 μ U/mL

Matched **1:2** using Nearest Neighbor Matching

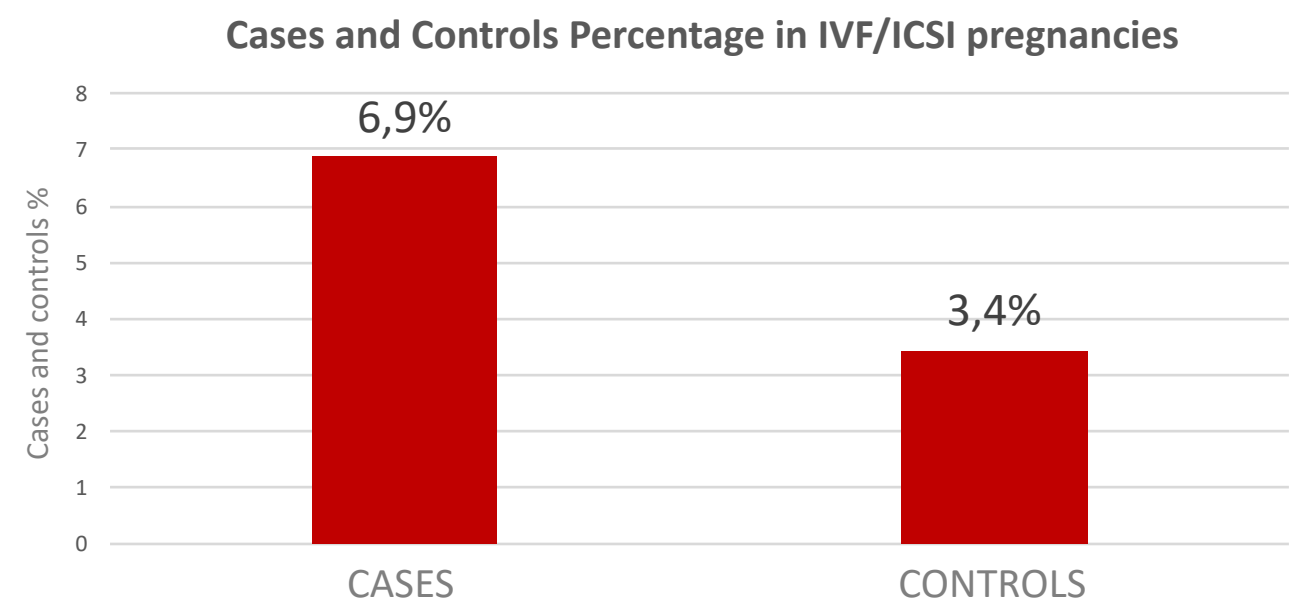
Data collection: Extracted from hospital databases

RESULTS

Among **2,610 eligible newborns**, the overall incidence of elevated **TSH (≥ 6 μ U/mL) at 48–72 hours** of life was **2.9%**. After matching the patients for maternal, perinatal and neonatal variables, the sample size of the study included:

MODE OF CONCEPTION in Relation to Neonatal TSH Levels

	Total N= 393	Cases N=131 (33.3%)	Controls N=262 (66.6%)	P
Mode of conception [n (%)]				
Spontaneous	370 (94.1)	122 (93.13)	248 (94.66)	0.2
IVF/ICSI	18 (4.6)	9 (3.44)	9 (3.44)	
IUI	5 (1.3)	0 (0.0)	5 (1.91)	



ART-RELATED FACTORS in Relation to Neonatal TSH Levels

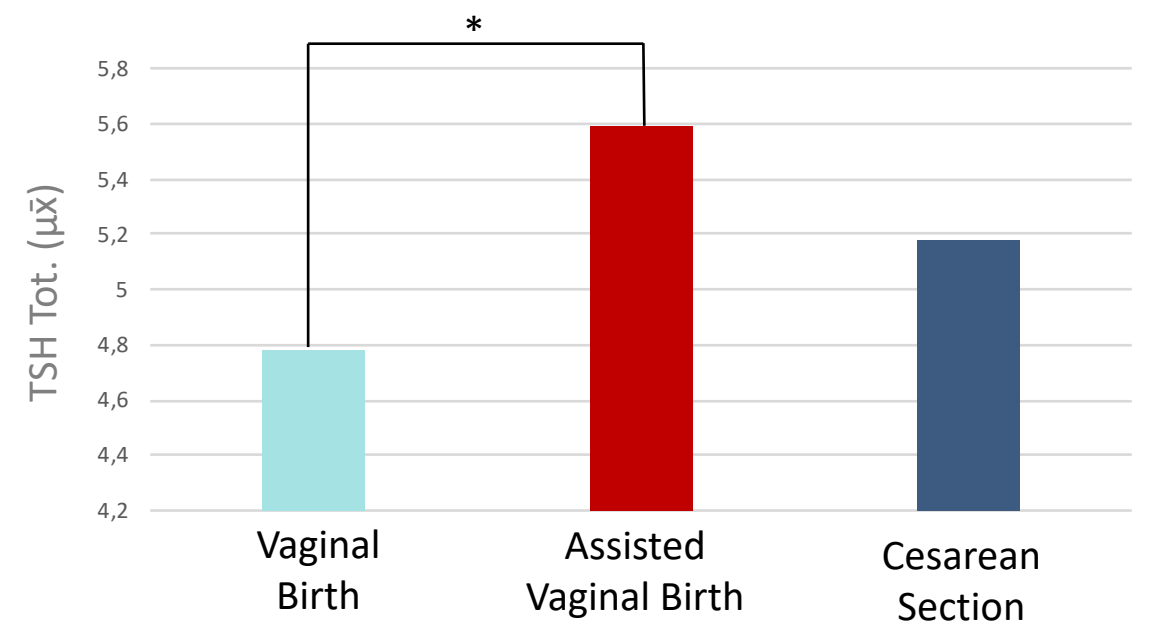
	IVF/ICSI Total n=18	IVF/ICSI Cases n=9 (50%)	IVF/ICSI Controls n=9(50%)	P
Gametes [n (%)]				
Homologous	17 (94.4)	8 (88.9)	9 (100)	1.00
Heterologous	1 (0.06)	1 (11.1)	0 (0.0)	
Technique [n (%)]				
IVF	9 (50.0)	6 (66.7)	3 (33.33)	0.34
ICSI	9 (50.0)	3 (33.33)	6 (66.66)	
Transfer [n (%)]				
Fresh	15 (83.3)	7 (77.8)	8 (88.9)	1.0
Frozen	3 (16.7)	2 (22.2)	1 (11.1)	
ET/cycle [n (%)]				
1	14 (88.9)	8 (88.9)	8 (88.9)	1.0
2	2 (11.1)	1 (11.1)	1 (11.1)	
Transfer day [x̄ (SD)]	5.22 (0.5)	5.0 (0.0)	5.33 (0.5)	0.06

	Total IVF/ICSI with known stimulation n=17	IVF/ICSI Cases with known stimulation n=8 (47%)	IVF/ICSI Controls with known stimulation n=9 (53%)	P
Protocol [n (%)]				
Agonist short	1 (5.8)	0 (0.0)	1 (11.1)	0.57
Agonist long	3 (17.6)	2 (25)	1 (11.1)	
Fixed antagonist	10 (59)	4 (50)	6 (66.7)	
Trigger [n (%)]				
Flexible antagonist	3 (17.6)	2 (25)	1 (11.1)	0.23
hCG 10000 UI	8 (47.0)	2 (25.0)	6 (66.7)	
hCG 5000 UI	8 (47.0)	5 (63.5)	3 (33.3)	
Triptorelin 0,2 mg	1 (5.8)	1 (12.5)	0 (0.0)	

Comparison of Neonatal TSH Levels by MODE OF DELIVERY

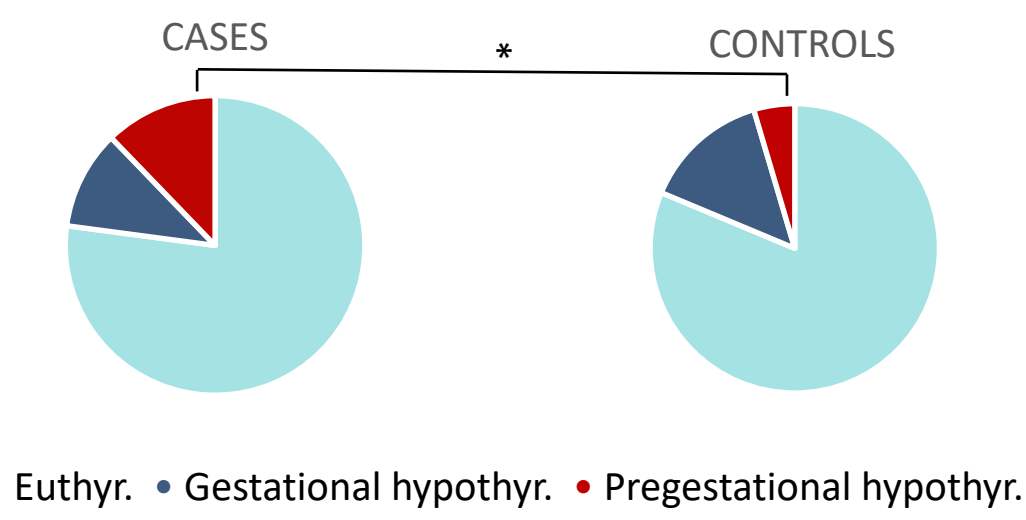
	VB N=297 (75.6%)	AVD N=30 (7.6%)	CS N=66 (16.8%)	P (VB vs. AVD)	P (VB vs. CS)	P (AVD vs. CS)
TSH (μU/mL)						
Cases [x̄ (DS)]	7.25 (1.4)	6.89 (0.75)	8.28 (4.0)	/	/	/
Controls [x̄ (DS)]	2.33 (1.3)	4.20 (1.6)	2.09 (1.3)	/	/	/
Tot. (μ x (DS))	4.78 (1.6)	5.59 (2.6)	5.18 (1.8)	0.002*	0.213	0.132

VB = Vaginal Birth; AVD = Assisted Vaginal Delivery, CS = Cesarean Section



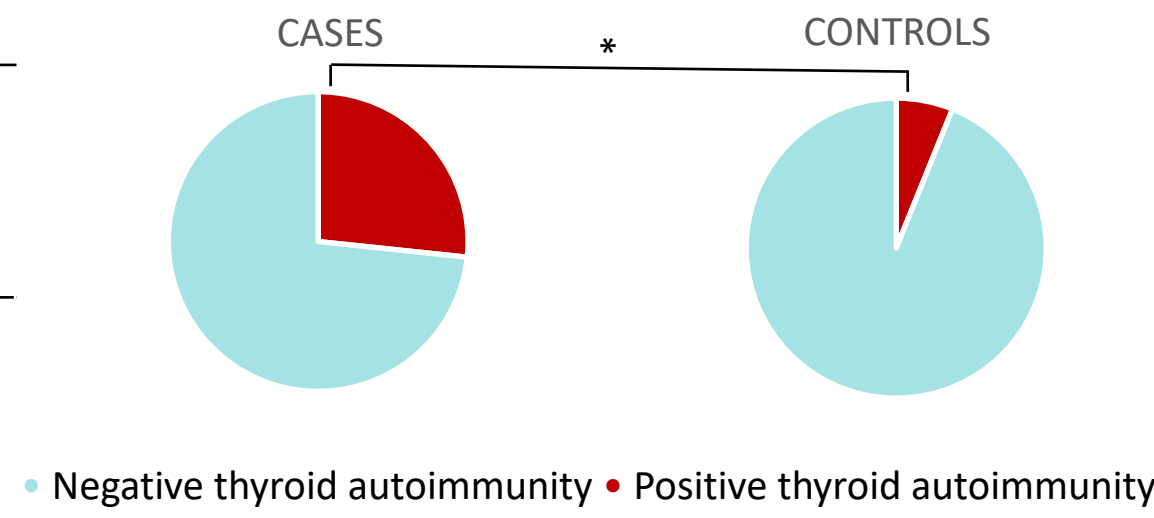
MATERNAL THYROID FUNCTION in Relation to Neonatal TSH Levels

	TOTAL N= 393	CASES N=131 (33.3%)	CONTROLS N=262 (66.6%)	P
Thyroid function [n (%)]				
Euthyroidism	314 (79.9)	101 (77.7)	213 (82.6)	0.017*
Gestational hypothyroidism	51 (13.0)	14 (10.7)	37 (14.3)	
Pregestational hypothyroidism	28 (7.1)	16 (12.2)	12 (4.7)	



MATERNAL THYROID AUTOIMMUNITY in Relation to Neonatal TSH Levels

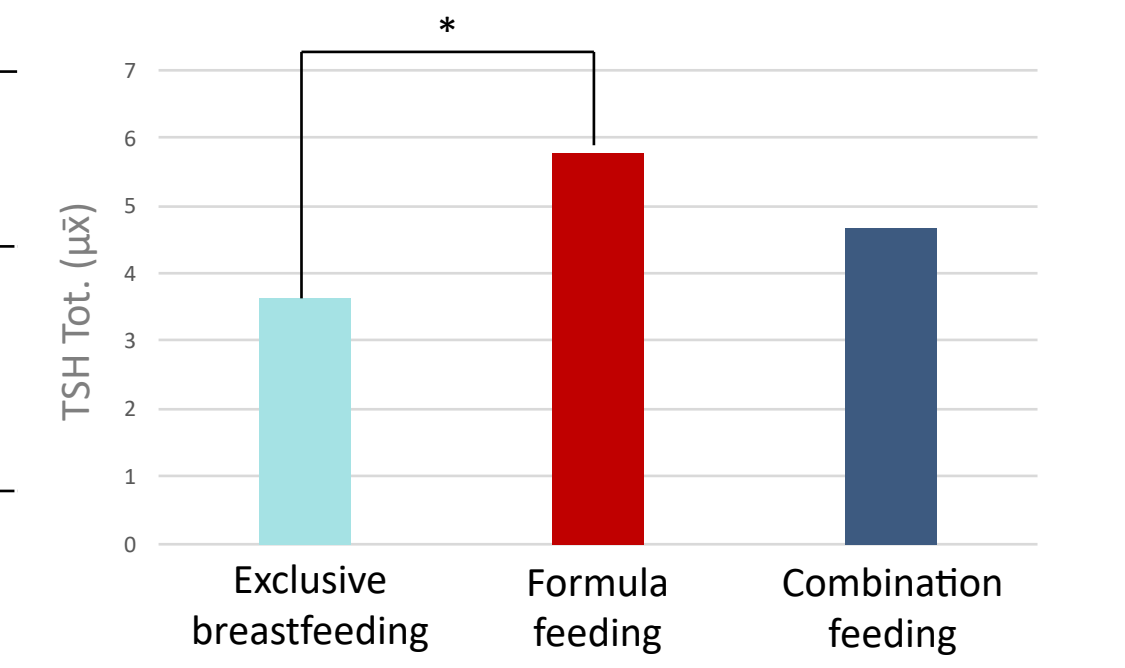
	TOTAL Hypothyroid patients n = 79	CASES Hypothyroid patients n= 30 (38%)	CONTROLS Hypothyroid patients n= 49 (62%)	P
Thyroid autoimmunity [n (%)]				
Positive	11 (13.9)	8 (26.7)	3 (6.1)	0.026*
Negative	68 (86.1)	22 (73.3)	46 (93.9)	



Comparison of Neonatal TSH Levels by FEEDING METHOD

	EB N=258 (65.7%)	FF N=126 (32%)	CF N=9 (2.3%)	P (EB vs. FF)	P (EB vs. CF)	P (FF vs. CF)
TSH (μU/mL)						
CASES [x̄ (DS)]	6.13 (1.1)	8.88 (3.1)	7.00 (1.1)	/	/	/
CONTROLS [x̄ (DS)]	1.15 (1.4)	2.68 (1.2)	2.34 (1.00)	/	/	/
TOT (μ x (DS))	3.64 (2.4)	5.78 (3.72)	4.67 (2.1)	0.012*	0.320	0.542

EB = Exclusive Breastfeeding; FF= Formula Feeding; CF = Combination Feeding



CONCLUSIONS AND CLINICAL IMPLICATIONS

Although mode of conception and ART were not associated with elevated neonatal TSH at 48-72h, several maternal and perinatal factors - namely **maternal pregestational thyroid dysfunction**, **maternal thyroid autoimmunity**, **operative delivery**, and **neonatal formula feeding** – showed independent links to higher neonatal TSH values. These findings underscore the need for tailored neonatal screening strategies, particularly in at-risk subgroups, regardless of the conception method.

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