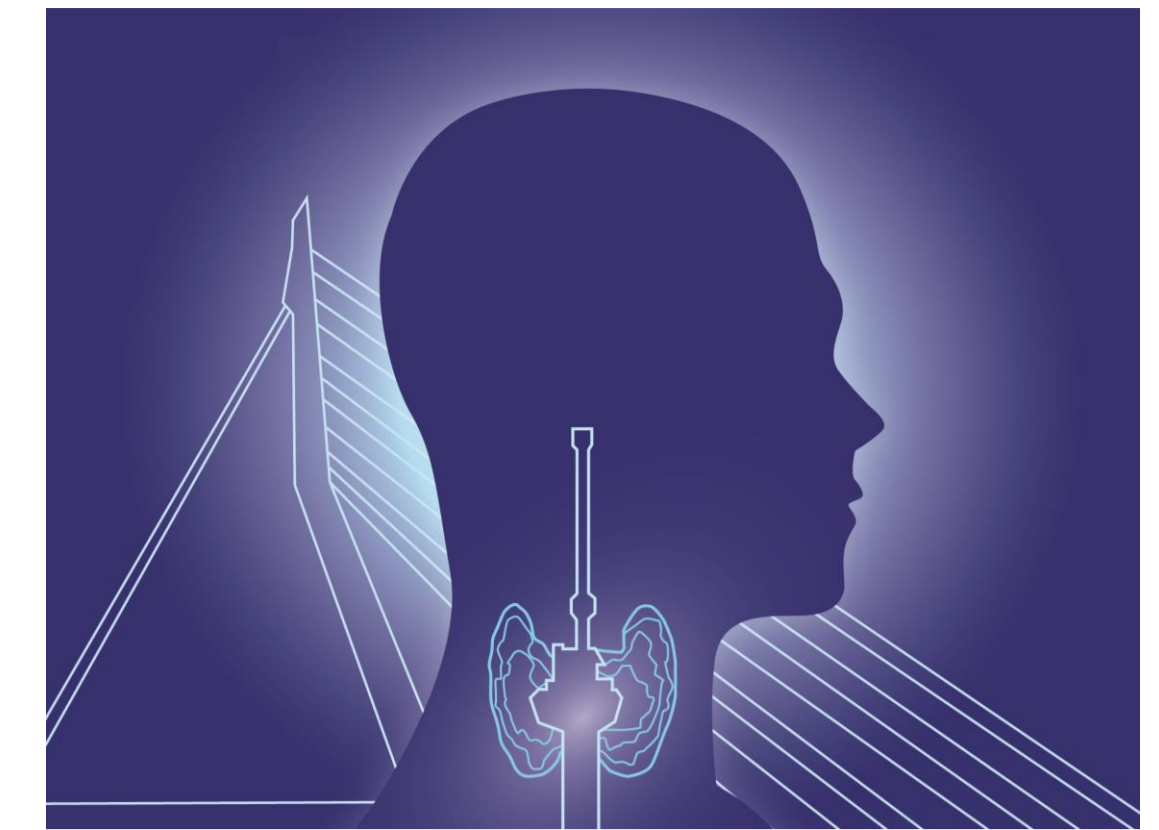


# hCG levels are essential for the correct interpretation of gestational TSH levels: the clinical risk assessment of premature delivery.

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## Introduction

High maternal TSH and/or low FT4 during pregnancy is associated with an increased risk of premature delivery. hCG is the main determinant of thyroid function changes during pregnancy but has a versatile pattern with high inter and intra-individual variability. The amount of hCG that is present during TSH or FT4 measurement is a proxy for the amount of thyroid stimulation. The extent of stimulation changes the expected TSH or FT4 level. A relative thyroid dysfunction may be present particularly women with the combination of high hCG levels and high TSH or low FT4 levels. We hypothesized that the correct interpretation of thyroid function tests and its use in the risk assessment of premature delivery during pregnancy depend on hCG levels.

## Methods & Participants

TSH, FT4, hCG and TPO-antibody levels were available in 5956 women. In logistic regression models non-linearity was assessed using restricted cubic splines and accordingly we tested for between TSH or FT4 and hCG in the risk for premature delivery - when significant analyses were stratified. All analyses were adjusted for maternal age, smoking, education level, ethnicity, parity, BMI, height and fetal gender.

## Results

- Only the association between TSH levels and premature delivery was different according to hCG levels (Table 1).
- Figure 1 shows how the risk of premature delivery differs according to various combinations of hCG and TSH levels.
- Table 2 shows the odds ratio for premature delivery according to high TSH levels for the whole group ('Overall') and stratified according to different hCG levels.
- We found that women with TSH levels within the normal range accompanied with high hCG levels had an up to 6-fold increased risk of premature delivery.
- Women with similar TSH levels but low hCG did not have an increased risk.

Figure 1. The risk of premature delivery according to hCG and TSH

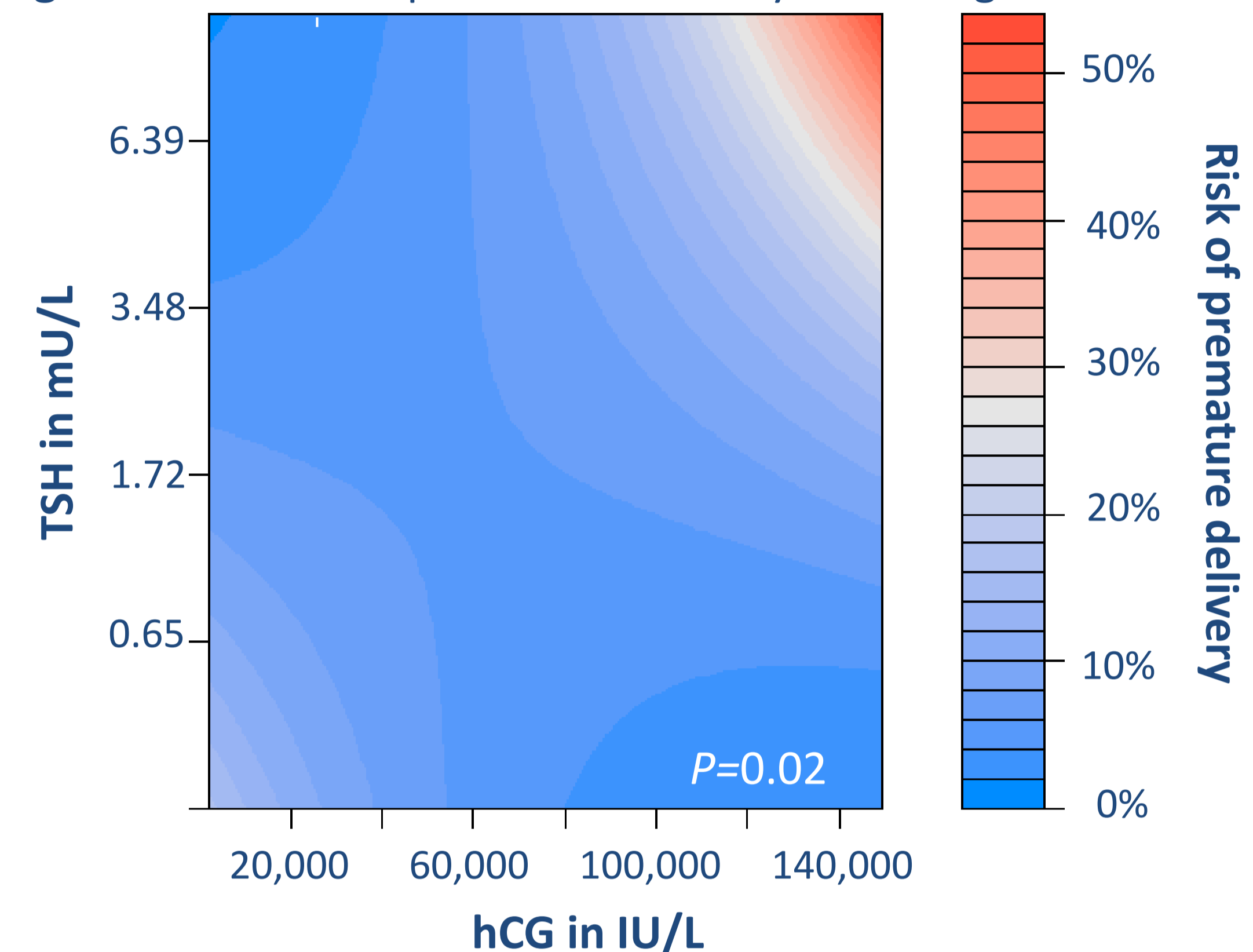


Table 1. Interaction between TSH or FT4 and hCG for the risk of premature delivery.

Variable in model	Premature delivery	
	$\beta$	P-value
TSH	-0.024	0.86
hCG	-0.180	0.13
TSH + hCG	-0.073 + -0.0150	0.85 + 0.13
TSH * hCG	0.125	0.02
FT4	-0.244	0.32
hCG	-0.180	0.13
FT4 + hCG	-0.205 + -0.140	0.47 + 0.15
FT4 * hCG	-0.514	0.64

hCG betas are per 10,000 IU/L - Table 1 shows the P-values for the linear association between TSH, hCG or their product interaction term and premature delivery (<37 weeks gestation). All analyses were adjusted for maternal age, smoking, education level, ethnicity, parity, BMI, height and fetal gender. These results remained similar amongst TPOAb negative women only, or amongst women with spontaneous premature delivery.

Table 2. Outline of the interaction between hCG and TSH in the risk of premature delivery.

% Cut-off TSH (mU/L)	Overall	<20,000	20,000-30,000	30,000-40,000	40,000-50,000	50,000-60,000	60,000-70,000	70,000-80,000	>80,000
≥ 96 (4.02)	1.88 (1.14-3.12)	*	1.13	1.30	1.47	1.36	6.07	5.42	5.28
≥ 95 (3.72)	1.62 (0.98-2.67)	*	0.82	1.00	1.21	1.25	3.50	5.47	6.07
≥ 94 (3.49)	1.50 (0.95-2.35)	0.78	0.64	0.91	1.03	1.47	2.81	5.21	5.18
≥ 93 (3.32)	1.40 (0.92-2.12)	0.65	0.56	1.02	1.34	1.30	2.42	3.59	4.64
≥ 92 (3.15)	1.28 (0.85-1.92)	0.54	0.49	1.07	1.14	1.54	2.32	3.63	3.91
≥ 91 (3.01)	1.18 (0.79-1.74)	0.45	0.45	1.34	1.00	1.19	2.10	3.34	3.30
≥ 90 (2.91)	1.24 (0.85-1.80)	0.39	0.51	1.15	1.25	1.46	1.98	4.63	3.06
≥ 89 (2.81)	1.16 (0.80-1.69)	0.34	0.51	1.20	1.11	1.33	1.80	3.78	2.79
≥ 88 (2.73)	1.23 (0.87-1.75)	0.43	0.64	1.08	1.13	1.22	3.34	3.13	2.61
≥ 87 (2.66)	1.22 (0.85-1.74)	0.49	0.61	1.01	1.06	1.42	2.96	2.95	2.43
≥ 86 (2.59)	1.16 (0.82-1.64)	0.45	0.59	0.92	1.16	1.24	2.71	2.85	2.33
≥ 85 (2.53)	1.10 (0.77-1.56)	0.58	0.53	0.85	1.16	1.13	2.44	2.70	2.02

\* None of the women in this subgroup had a premature delivery.

Table 2 shows the adjusted odds ratio for premature delivery (<37 weeks) according to different percentile cut-offs for TSH, stratified by concomitant hCG levels. All analyses were adjusted for maternal age, smoking, education level, ethnicity, parity, BMI, height and fetal gender. hCG cut-off groups were not associated with the risk of premature delivery.

## Conclusions

- The addition of hCG may improve the risk assessment of premature delivery according to TSH.
- High TSH levels despite high hCG levels reflect the inability of thyroid function to increase according to hCG stimulation.
- This inability to increase thyroid function is a novel risk factor for premature delivery.
- Future studies are needed to replicate these results and incorporate these findings into clinical decision models.

