

# Characteristics and Outcome of Neonates with Congenital Hypothyroidism Born after In Vitro Fertilisation (IVF)

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## Background knowledge

In vitro fertilisation (IVF) has been widely used during the last decades. Increased susceptibility to birth defects and a higher cardiometabolic risk in children born after IVF than naturally conceived (NC) children have been reported. Also, a higher incidence of hyperthyrotropinemia has been noted in children born after IVF with respect to NC children and has been attributed to an epigenetic modification of the TSH set-point.

The **National Greek Neonatal CH screening program** was initiated in 1980 and is carried out by a **single laboratory** that receives and tests the Guthrie cards from all maternity hospitals. The program initially covered the Athens Metropolitan area but quickly expanded and covered the entire country. Over the last 35 years, more than **3,690,000 neonates** have been screened using a variety of TSH screening methods.

## Objective and hypothesis

To retrospectively evaluate the main characteristics and outcome of children born after IVF and diagnosed with CH.

## Patients and Methods

Data from the medical records of children diagnosed with CH by the Greek Neonatal CH screening program were reviewed.

## Results and Discussion

A total of **1474** children with CH were analyzed. Of these, 200 neonates (**13.5%**) were born following IVF (117 boys and 83 girls; ratio 1.4:1). 80% of neonates born after IVF were multitons, 85% were premature (<37 gestational week) and 82% had a birth weight below 2500gr (**Table 1** and **Figure 1**).

**TSH values at diagnosis:** 15% had a TSH > 20 mIU/L, 26% between 10 and 20 mIU/L and 59% below 10 mIU/L (mean 36.1 ± 115 mIU/L). The probability of CH to be transient is inversely related to the initial TSH values in females whereas in males seems independent (**Figure 2**).

**Gestational age:** 57% of neonates were moderate to late preterm and 28% were very to extreme preterm. The probability of CH to be transient is inversely related to the weeks of gestation in females whereas in males the percent is more consistent between subgroups (**Figure 3**).

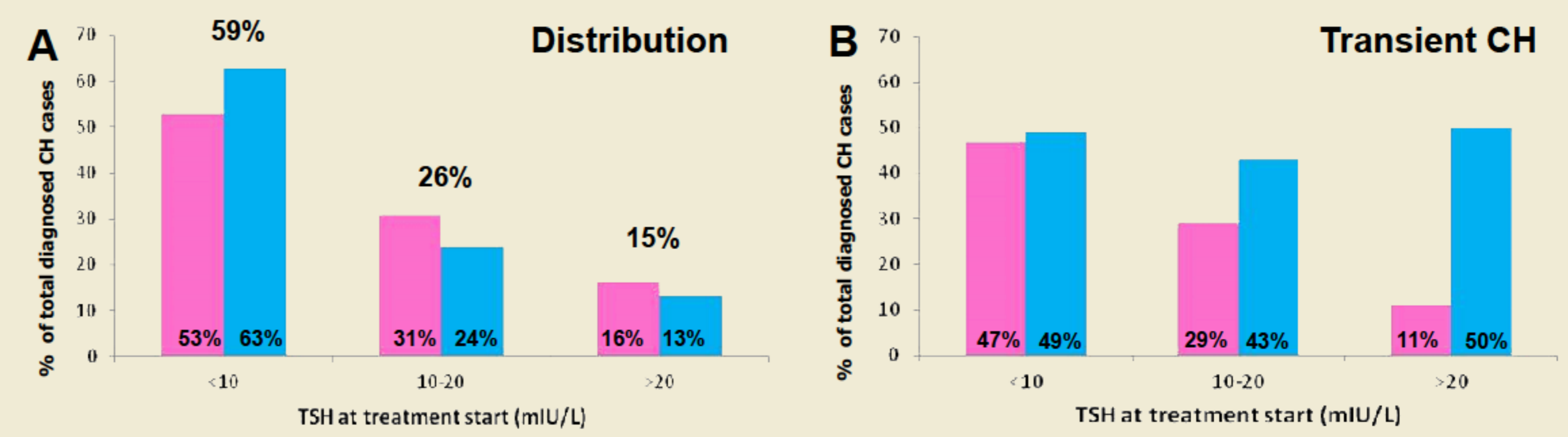
**Thyroid ultrasonography:** imaging data were available to analyze in 156 patients. Diagnoses were categorized as normal, ambiguous or as anatomical defect (absence, ectopy etc). A diagnosis of "ambiguous" was used in the case of very small thyroid glands, low normal size of thyroid with respect to age, prominent heterogeneity etc. In only 5% of CH patients born after IVF ultrasonography revealed an anatomical defect of the thyroid gland (**Figure 4**).

Pertinent **long-term data** were available in 141 patients (81 boys and 60 girls). Their age at the time of the analysis was 7.53 ± 3.1 yrs (>1 year: 140, > 3 yrs: 133) With respect to the **outcome**, the overall percent of **permanent CH** was **56%**, 51% in males and 63% in females and of **transient CH** was **44%**, 49% in males and only 37% in females (**Table 1**).

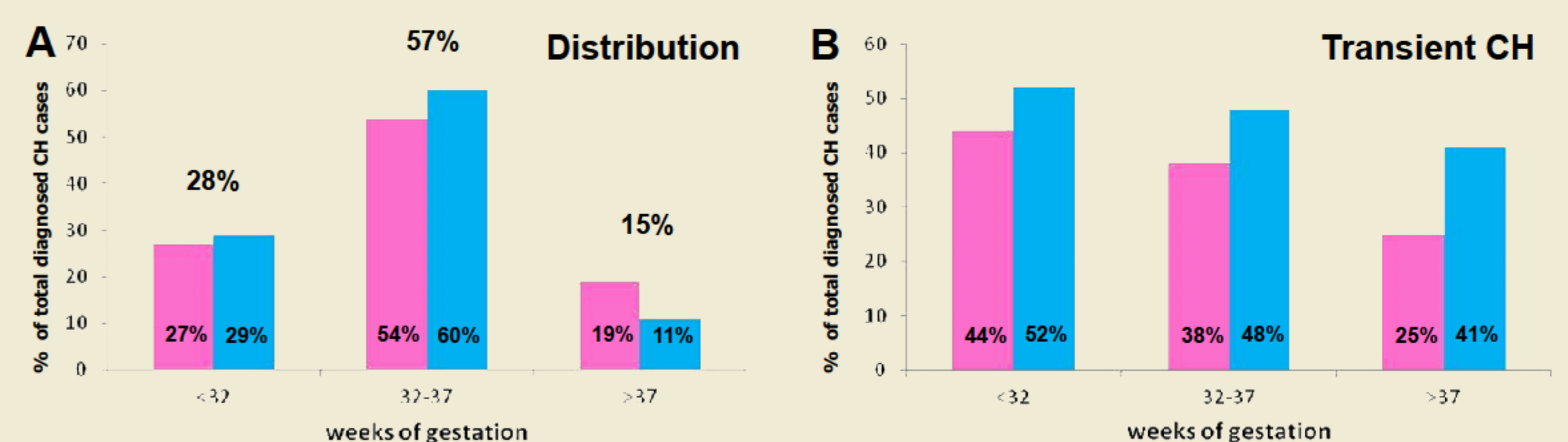
Group	Males	Females
Total	200	117
Start >6m	20	11
Long term data unavailable	22	16
Characterization impossible	17	9
Thyroid anatomical defect	9	3
LT4 dose increase	35	20
LT4 stop unsuccessful	36	19
LT4 stop successful	61	39
<b>Permanent CH</b>	<b>80</b>	<b>38</b>
<b>Transient CH</b>	<b>61</b>	<b>22</b>
Total	141	60

**Table 1:** CH patients born after IVF that were included in the study. The overall percent of **transient CH** was 44% (males: 49%, females: 37%)

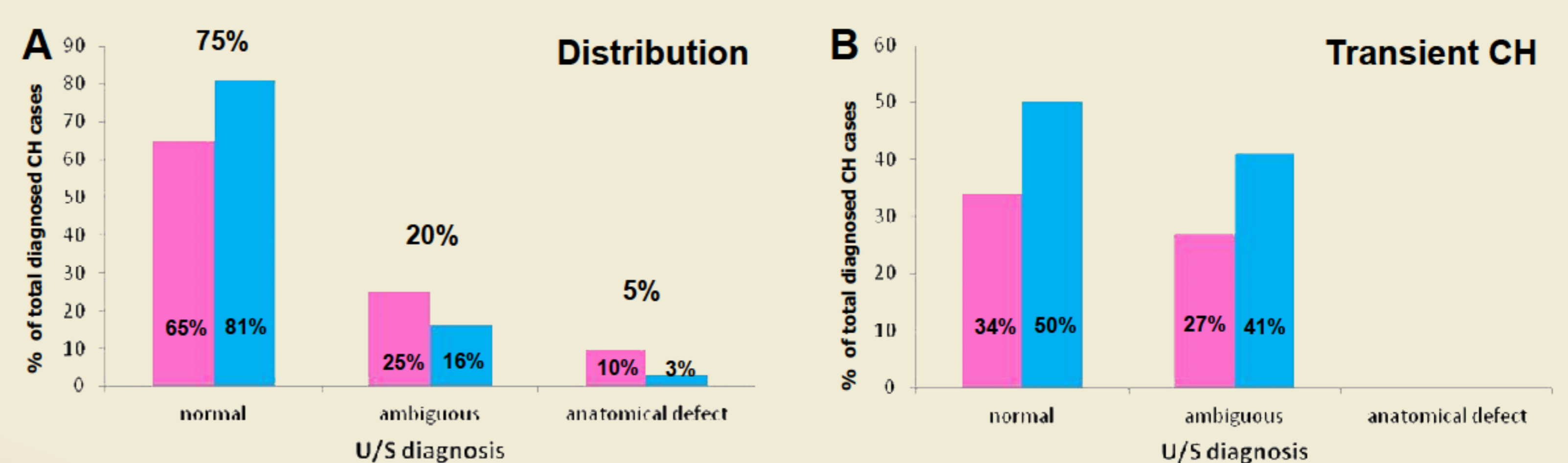
**Figure 1:** Demographic data of CH patients born after IVF: A male predominance is observed (boys to girls ratio 1.4:1). Most of the children were born prematurely (85%) with a low birth weight (82%) following high risk pregnancies (multitons 80%)



**Figure 2:** (A) The distribution of CH neonates born after IVF with according to TSH values at diagnosis. Data depicted as percent of total number of **females** (pink) or **males** (blue), respectively. Overall (shown on top), 59% of patients had an initial TSH <10 mIU/L, 26% between 10-20 mIU/L and 15% >20 mIU/L. Most of CH patients born after IVF had mild hypothyroidism at diagnosis (B) Transient CH (shown as percent within each TSH subgroup) in **female** (pink) and **male** (blue) CH neonates born after IVF with respect to TSH values at diagnosis. The probability of CH to be transient is inversely related to the initial TSH values in females whereas in males seems independent.



**Figure 3:** (A) The distribution of CH neonates born after IVF with according to gestational age (in weeks). Data depicted as percent of total number of **females** (pink) or **males** (blue), respectively. Overall (shown on top), 28% of patients were born <32 wks, 57% between 32-37 wks and 15% born >37 wks. Most of CH patients born after IVF are premature neonates (B) Transient CH (shown as percent within each gestational age subgroup) in **female** (pink) and **male** (blue) CH neonates born after IVF with respect to weeks of gestation. The probability of CH to be transient is inversely related to the weeks of gestation in females whereas in males the percent is more consistent between subgroups.



**Figure 4:** (A) The distribution of CH neonates born after IVF with according to ultrasonographic (U/S) diagnosis. Data depicted as percent of total number of **females** (pink) or **males** (blue), respectively. Overall (shown on top), in 75% of patients the thyroid gland was considered as normal, in 20% ultrasonographic data were categorized as ambiguous and in only 5% anatomical defects were apparent. A diagnosis of "ambiguous" was used in the case of very small thyroid glands, low normal size of thyroid with respect to age, prominent heterogeneity etc (B) Transient CH (shown as percent within each U/S subgroup) of **female** (pink) and **male** (blue) CH neonates born after IVF with respect to weeks of gestation.

## Conclusions

Children born after IVF constitute a relatively large subgroup (13.5%) of children with CH, with a notable male predominance (1.4:1). Most of the children were born prematurely (85%) with a low birth weight (82%) following high risk pregnancies (multitons 80%). Anatomical thyroid defects are rare (present in only 5% of patients). Although hypothyroidism at diagnosis is mild based on TSH values, in 50% of males and 63% of females born after IVF, a certain degree of dysfunction of the Hypothalamic-Pituitary-Thyroid-axis seems to persist. The reason of the gender dimorphism with respect to the diagnosis and outcome is not apparent.

