**הגשת הצעה לביצוע עבודה בהתנסות מחקרית**

1. **שם הסטודנט** – לינוי דרוקר
2. **שנת לימודים** -רביעית
3. **סוג העבודה**: עבודת מחקר קליני.
4. **שם העבודה בעברית**:

הבדלים בשיעור היפותיאורידיזם מולד בין קבוצות אתניות שונות בדרום ישראל

1. **שם העבודה באנגלית**:
2. Ethnic differences in the rates of congenital hypothyroidism in the population of southern Israel
3. **שם המדריך הראשי ותפקידו האקדמי** - פרופסור אליהו הרשקוביץ, מס' זהות -
4. **מדריך נוס**ף - ד"ר אלון חיים, מס' זהות -
5. **מקום ביצוע העבודה**: חטיבת הילדים, במרכז הרפואי סורוקה .
6. מילות מפתח: children , epidemiology, southern Israel, congenital hypothyroidism

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

חתימה, ד"ר אלון חיים

**מדריך נוסף**

חתימה, פרופ' אליהו הרשקוביץ

**מדריך ראשי**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

חתימה,

**סטודנט**

תאריך משוער להתחלת העבודה:

תאריך משוער לסיום העבודה:

Thyroid hormones are necessary for the development of tissues, including brain and skeletal tissues, and for normal growth (1). The hormones affect genes that are essential for neural development in a limited window of time, and even a short-term hormone deficiency can cause irreversible brain damage (1). It should be kept in mind that brain development in the first trimester of pregnancy is entirely dependent on the mother’s thyroid function (1). Congenital hypothyroidism (CH) treatment is one of the most common ways of preventing mental retardation, but early diagnosis is needed (1).

The most common cause of CH is dysgenesis of the thyroid gland (5). The clinical manifestations of hypothyroidism vary and are caused by two main effects of lower levels of thyroid hormones: decrease in overall metabolism and accumulation of matrix glycosaminoglycans in the interstitial spaces of various tissues (2). Congenital hypothyroidism is asymptomatic in 95% of newborns in the first hours of life, due to maternal thyroxine (T4) that crosses the placenta and accounts for 25% to 50% of required T4 (5). Symptoms of CH include feeding problems, lethargy, hoarse cry, macroglossia, constipation, puffy (myxedematous) and/or coarse facies, large fontanels, hypotonia, dry skin, hypothermia, and prolonged jaundice, primarily caused by unconjugated hyperbilirubinemia (5).

Congenital hypothyroidism can have dramatic effects on infant development and can cause developmental delay and cognitive issues (6). Most CH cases are sporadic; therefore, it is difficult to predict which infants are likely to be affected (5).The incidence of hypothyroidism is higher for newborns with very low birth weight; immaturity of the hypothalamic-pituitary-thyroid axis will lead to delayed postnatal increase in thyroid-stimulating hormone (7).

Because hypothyroidism is treatable and its effects can be prevented, newborn screening programs (6) have been developed in which thyroid hormone levels are measured from dried blood spotted on filter paper generally at least 36 hours to two days after birth for full-term infants (2,5).

For preterm infants, there are three main techniques. The first technique is to give the thyroid-stimulating hormone (TSH) test to children who score in the lowest 10% in the initial test of free T4 (fT4). The second technique is to give both the T4 and TSH tests simultaneously. The third technique is to extract TSH from the blood assay (2). In the United States, initial T4 follow-up testing is the most common program (2). Infants with a TSH value greater than 30 mU/L in serum units are called for examination in the clinic at about one week of age (2).

The screening test is routinely performed today in the United States, Canada, Europe, Israel, Japan, Australia, and New Zealand, as well as in other countries in Eastern Europe, South America, Asia, and Africa (6).

Treatment for hypothyroidism is normally initiated when whole-blood serum TSH concentration is greater than the normal limit for age. In addition, when the concentration of fT4 is less than the normal limit for age, treatment is initiated without reference to TSH levels (9).

The incidence of CH, as diagnosed after clinical manifestations, was initially reported in the range of 1 in 7,000 to 1 in 10,000 infants worldwide (4). During the past few decades, the apparent incidence has increased to about 1 in 2,372, as was reported in the United States (4). One possible explanation is that more-sensitive screening algorithms have resulted in the detection of milder cases of hypothyroidism (4). Furthermore, there is some variation in the prevalence among different ethnic and racial groups (4). Approximately 85% of cases of CH are sporadic, and 15% are hereditary (5,6).

The prevalence of CH varies in different areas of the world and in different points in time. In a study of the Canadian population that was published in the The Journal of Clinical Endocrinology & Metabolism, the authors found that the prevalence of hypothyroidism increased because of minimal changes in the TSH screening cutoff (10). Other factors that affect CH prevalence include the ethnic composition of different populations and changes in them over time. A study performed in New Zealand found that the incidence of CH went up from 2.6 to 3.6 per 10,000 live births in 2012. The incidence was not a result of an increase in thyroid dysgenesis but of change in the country’s ethnic composition: there was a twofold increase in newborns of Asian descent and a 40% increase in newborns of Pacific Island descent. The study found that genetics, not change in environmental conditions, appeared to influence the expression of hormonal dysfunction (11). Furthermore, it was found that between 1978 and 2005, the prevalence of CH in New York State increased by 138%, and it was observed that among races and ethnicities, Asians have a much greater incidence of CH (12).

Another study, conducted in a university research center and based on 26 Sudanese families, found that thyroglobulin (TG) gene mutations were significantly higher on average in the Sudanese compared to the average number of TG mutations in other populations. These mutations occur in domains important for protein structure and function, predicting the CH phenotype. The higher prevalence of TG gene mutations is a result of gene length and possible positive genetic selection caused by endemic iodine deficiency (13). Furthermore, in the past decade, the prevalence of hypothyroidism has increased. Of 947,258 newborns screened between 2009 and 2018 in China, 829 (406 girls) were diagnosed with CH at birth (1/1136). Also, of 608 cases of CH diagnosed at birth and reassessed at the age of 3 years, 121 were transient and 487 were permanent. This article argues that preterm birth and low birth weight also impact CH (14). In addition, a five-year study in Iran found that the prevalence of CH is higher than in other countries; of 86,567 neonates tested, 194 were confirmed to have CH (15).

In Israel, consanguinity is common. From November 2009 to January 2010, the percentage of marriages between family members was 44.8%. The most prevalent type of consanguinity is between cousins (3).Consanguinity has been proven to contribute to high rates of birth defects and genetic diseases, resulting in high infant mortality.

Following the above, in this study we decided to compare the prevalence of CH between the Bedouin population and the Jewish population in the Negev.

**Research Goals**

1. **Main goal**

* To examine whether there is a difference in the incidence of congenital hypothyroidism between the Bedouin population and the Jewish population in the Negev

1. **Secondary goals**

* To compare the rate of hypothyroidism in the southern region with the whole country
* To investigate the demographic features of congenital hypothyroidism

**Research Hypothesis**

The incidence of congenital hypothyroidism among the Bedouin population is higher than in the Jewish population.

**Research Methodology**

A retrospective study involving children with congenital hypothyroidism who were born between the years 2008 and 2016 in Soroka Medical Center

**Research Population**

1. **Inclusion criteria**

* Patients of Soroka Medical Center who were born with congenital hyperthyroidism between the years 2008 and 2016
* Patients who received treatment after age 3

1. **Exclusion criteria**

**Type of Study**

Retrospective cohort-based comparative study

* The following retrospective data will be collected from the Soroka Medical Center medical record and the national newborn screening program:

-Maternal hypothyroidism

-Sibling hypothyroidism

-Persistent goiter

-Persistent antibodies

-Congenital hypothyroidism etiology

-Pregnancy data (gestational diabetes): week and birth weight

-Demographic details: gender, date of birth, ethnicity, place of residence

-Additional illnesses and/or regular medication

**Analysis of Results**

**Estimated Schedule**

**Student Roles**

* Review recent articles and studies, plan the study, and prepare a study proposal
* Take part in the statistical analysis with the help of a statistician
* Review and summarize the conclusions and results of the study
* Write a scientific article

References

1. Maria Segni MD. Congenital hypothyroidism. . 2019. <https://www.endotext.org/chapter/congenital-hypothyroidism/>.

2. LaFranchi S, Kirkland JL, Garcia-Prats JA, Hoppin AG. Clinical features and detection of congenital hypothyroidism. *UpToDate.Waltham, MA: UpToDate*. 2009.

3. Wasef Na’amnih, Orly Romano-Zelekha, Ahmed Kabaha, Liza Pollack Rubin, Natalya Bilenko, Lutfi Jaber, Mira Honovich, and Tamy Shohat. Bedouin population. . 2014. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159474/>.

stylefix

4. Aminzadeh M. Higher prevalence of permanent congenital hypothyroidism in the Southwest of Iran mostly caused by dyshormonogenesis: a five-year follow-up study. Arch Endocrinol Metab. 2018;62(6):602-8.

5. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet journal of rare diseases. 2010 Jun 10,;5(1):17.

4. LaFranchi S. Acquired hypothyroidism in childhood and adolescence. Up-ToDate (Consultado el 3 de agosto de 2015). 2007.

5. LaFranchi S, Kirkland JL, Garcia-Prats JA, Hoppin AG. Clinical features and detection of congenital hypothyroidism. UpToDate.Waltham, MA: UpToDate. 2009.

6. LaFranchi S, Kirkland J, Hopping A. Treatment and prognosis of congenital hypothyroidism. UpToDate.Waltham, MA. 2010.

7. Bijarnia S, Wilcken B, Wiley V. Newborn screening for congenital hypothyroidism in very-low-birth-weight babies: the need for a second test. J Inherit Metab Dis. 2011 Jun;34(3):827-33.

8. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism. J Clin Endocrinol Metab. 2014 /02/01;99(2):363-84.

9. Deladoëy J, Ruel J, Giguère Y, Van Vliet G. Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Québec. J Clin Endocrinol Metab. 2011 Aug;96(8):2422-9.

10. Albert BB, Cutfield WS, Webster D, Carll J, Derraik JGB, Jefferies C, et al. Etiology of Increasing Incidence of Congenital Hypothyroidism in New Zealand from 1993–2010. J Clin Endocrinol Metab. 2012 /09/01;97(9):3155-60.

11. Harris KB, Pass KA. Increase in congenital hypothyroidism in New York State and in the United States. Molecular Genetics and Metabolism. 2007;91(3):268-77.

12. Bruellman RJ, Watanabe Y, Ebrhim RS, Creech MK, Abdullah MA, Dumitrescu AM, et al. Increased prevalence of TG and TPO mutations in Sudanese children with congenital hypothyroidism. J Clin Endocrinol Metab. 2019 Dec 23,.

13. Chen J, Lin S, Zeng G, Wang W, Lin Z, Xu C, et al. EPIDEMIOLOGIC CHARACTERISTICS AND RISK FACTORS FOR CONGENITAL HYPOTHYROIDISM FROM 2009 TO 2018 IN XIAMEN, CHINA. Endocr Pract. 2020 Jan 22,.

14. Aminzadeh M. Higher prevalence of permanent congenital hypothyroidism in the Southwest of Iran mostly caused by dyshormonogenesis: a five-year follow-up study. Arch Endocrinol Metab. 2018;62(6):602-8.