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THE RELATION BETWEEN SEROLOGICAL HEPATOCYTE NUCLEAR FACTOR 1B (HNF 1B) GENE WITH GENITAL TRACT ANOMALIES

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ABSTRACT

Background: The hepatocyte nuclear factor 1B (HNF1B) gene are associated with various developmental anomalies, particularly in the genitourinary tract. This study evaluates the relation between serological HNF1B gene with genital tract anomalies. **Patients and Methods**: This cross sectional study was conducted at Baghdad Teaching Hospital from December 2023 to November 2024. A total of 50 participants with genital tract anomalies were screened for hepatocyte nuclear factor 1B (HNF1B) gene using 5ml from blood sample collected from participants for genetic analysis. Clinical and demographic data, also biochemical and imaging tests, were collected and analysed. **Results**: Among the participants, the most common anomalies were imperforate hymen (44%) and uterine agenesis with the absence of the upper two-thirds of the vagina (36%). HNF1B levels were statistically significantly in cases of ambiguous genitalia ($p < 0.0001$) and uterine agenesis ($p = 0.004$). However, no significant association was observed for other anomalies like high vaginal septum or cervical agenesis. **Conclusion**: There is a significant association between serological hepatocyte nuclear factor 1B (HNF1B) gene and certain congenital genital tract anomalies, particularly uterine agenesis and ambiguous genitalia, with elevated HNF1B levels observed in these conditions.

INTRODUCTION

The female reproductive system originates from four sources: mesoderm, primordial germ cells, coelomic epithelium, and mesenchyme. The uterus develops during Mullerian organogenesis, alongside the formation of the upper two third of the vagina, the cervix, and both fallopian tubes.[1]

All foetuses commence with undifferentiated gonads, which subsequently develop into either ovaries in females or testes in males. Despite being physically indistinguishable at this stage, unisex gonads are referred to as 'bipotential' due to their capacity to develop into either an ovary or a testis, contingent upon whether the individual has XX or XY chromosomes, respectively. The sex of the embryo is established by the genetic material from the sperm and egg during fertilization; however, foetal gonads do not develop male or female physical traits until the seventh week of gestation.[2]

During the fifth and sixth weeks of foetal development, the genital system remains undifferentiated. At this stage, two pairs of genital ducts are present: the mesonephric (Wolffian duct) and the paramesonephric (Mullerian duct).[3] In females, the lack of anti-Mullerian hormone (AMH) and the sex determining region Y gene (SRY) gene leads to the regression of Wolff ducts and the subsequent differentiation of Mullerian ducts. The upper portion of the vagina, cervix, both fallopian tubes, and uterus originate from the paramesonephric ducts In the seventh week, paired paramesonephric ducts emerge from localized invaginations of the coelomic epithelium located at the upper pole of each mesonephros; thereafter, the Müllerian ducts develop caudally and laterally towards the urogenital ridges.[3]

During the eighth week, a vertical fusion of the paramesonephric ducts transpires. The united cranial end originates the left and right components that will

eventually form the uterus. This structure comprises mesoderm that will develop into the endometrium and myometrium. The unfused cranial ends of the Mullerian ducts will differentiate into the fallopian tubes, whereas the fimbrial segment of the fallopian tubes originates from the open tip of this structure, which adopts a funnel form. The posterior segment of the united ducts will constitute the superior third of the vagina. At this juncture, a midline septum exists among these structures, and within the uterine cavity, this septum often undergoes complete reabsorption by approximately 20 weeks; however, it may linger, resulting in a septate uterus.[4] Concerning uterine ligaments, the round ligament and the ovarian ligament originate from the gubernaculum, with undifferentiated mesenchymal tissue affixed to the ovary in the female foetus. The round ligament must connect to both the ovary and uterus to properly position the ovary. By the conclusion of the first trimester, the development of the uterus and other structures originating from the Müllerian ducts is complete.[2]

This research aims to study the relation between serological hepatocyte nuclear factor 1B (HNF1B) gene among patients presenting with genital tract anomalies and identify the types of anomalies most commonly associated with these gene.

PATIENTS AND METHODS

Study Design, Setting and Data Collection Time

This study is designed as a cross sectional study was carried out at Baghdad Teaching Hospital-gynecological consultant clinic. In the period from December 2023 to November 2024. A sample of 50 ladies with genital tract anomalies will be assessed for eligibility and enrolled if they meet the inclusion criteria.

Ethical considerations and official approvals

Verbal permission was obtained from each patient prior to collecting data, and information was anonymous. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes. "Administrative approvals were granted from the following

The Council of Iraqi Board of Medical Specialization.

Approval and agreement of the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital.

Inclusion criteria

Patient age 14years old and above presented with primary amenorrhea with secondary sex characteristic.

- Patients diagnosed with one or more of the specified genital tract anomalies: Mullerian agenesis, cervical agenesis, unicornuate uterus, uterus didelphys, bicornuate uterus, septate uterus, longitudinal vaginal septum, transverse vaginal septum, or complex anomalies.
- Willingness to participate in the study and provide informed consent.

Exclusion criteria

Patients will be excluded from the study based on the following criteria:

- Presence of genital tract anomalies due to acquired conditions (e.g., surgery, trauma).
- Other congenital anomalies associated with genital anomalies like urinary or GIT anomalies (as the marker could be elevated due to the other anomalies).

Data collection and clinical assessment

50 patients are informed about the nature of the study.

Detailed history taken from all patients presented with primary amenorrhea and secondary sexual character included demographic data,. A comprehensive medical history was taken for each participant, focusing on their gynecological history, symptoms related to genital tract anomalies, and any previous diagnoses or treatments received for these conditions. Information on the participants' presentation, including the initial symptoms that led them to seek medical attention and the duration of these symptoms, was documented. Family history of same condition in other family member.

History & Examination

Menstrual History: Any history of cyclic abdominal or pelvic pain (suggesting obstructive anomalies like imperforate hymen or transverse vaginal septum).

Family History of same condition in other family member (history of primary amenorrhea, or infertility in relatives.

Associated Symptoms: Urinary symptoms (e.g., recurrent UTIs, dysuria) suggesting urological anomalies. Gastrointestinal symptoms (e.g., constipation).

Features of androgenization (hirsutism, deepening voice, clitoromegaly, acne).

Past medical and surgical history, Neonatal or childhood surgeries for ambiguous genitalia, surgeries or interventions for pelvic/abdominal issues.

Psychosocial History: Concerns regarding body image, emotional impact of amenorrhea, sexual history (marital state).

Physical Examination

Conduct the examination with sensitivity and ensure patient privacy.

General Examination: Height and weight, body mass index BMI (weight / heigh^2) for nutritional status.

Secondary sexual characteristics Tanner stage includes: Breast development, Pubic and axillary hair.

• Note discrepancies in breast and hair development that may indicate disorders of sexual development (DSD).

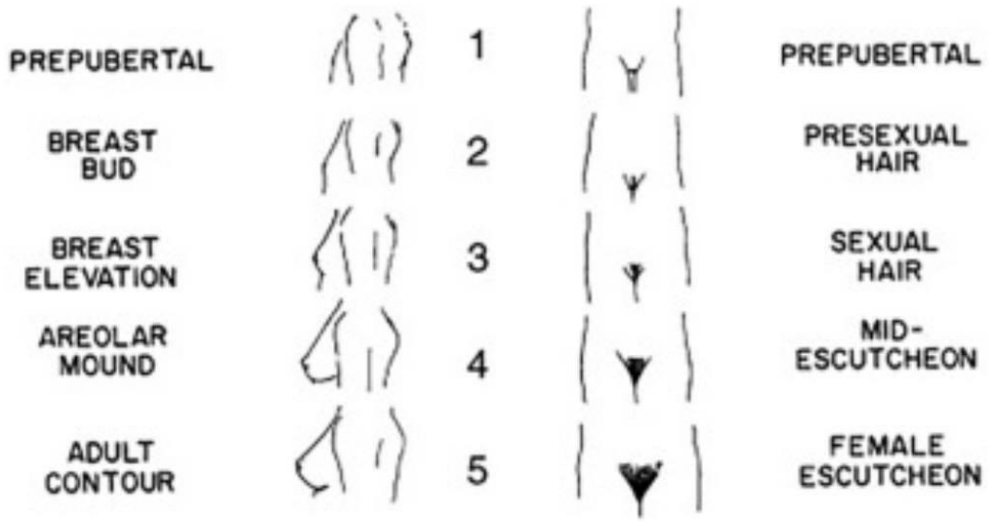

Figure 1: Tanner stage of breast and pubic hair.

Abdominal Examination: Look for any palpable masses (e.g., hematocolpos due to obstruction).Note any tenderness or distension.

Genital Examination

• External Genitalia: Presence and appearance of labia, clitoris, and vaginal introitus. Signs of androgen exposure (e.g., clitoromegaly).

• Internal Examination: Often deferred in virginal patients; consider ultrasound or MRI for visualization of uterus, ovaries or testes. Look for hymenal anomalies (e.g., imperforate hymen).

Other Signs

• Dysmorphic features (e.g., low-set ears, webbed neck in Turner syndrome).

• Signs of systemic diseases (e.g., hyperpigmented skin in CAH).

Method

The total sample size was 52 cases, two cases were excluded from the study as they have urinary tract abnormality (ipsilateral renal agenesis) diagnosed by ultrasound and MRI. The remaining cases included in the study were 50 cases.

Participants underwent a series of investigations to confirm the diagnosis of genital tract anomalies and to screen for HNF1B mutations. This included.

10 milliliters of venous blood sample was taken and sent for Biochemical test included: renal function test (blood urea and serum creatinine) and liver function test (alanine aminotransferase ALT, aspartate aminotransferase AST, alkaline phosphate ALP) and for karyotyping study.

5ml from blood samples were collected from participants for genetic analysis to detect mutations in the HNF1B gene using (Human Hepatocyte nuclear factor 1 beta (HNF1 BETA) ELISA Kit Catalog No: YLA3852HU). The genetic testing process involved sequencing of the HNF1B gene to identify any pathogenic variants.

Normal range

B.Urea 14.90 -40 mg/dl

S. creatine <0.90 mg/dl

AST up to 32 u/l

ALT up to 34 u/l

ALP: 53-128 u/L

HNF 1B: detection range 10-3000 ng/l.

- **Imaging Studies:** Transabdominal Ultrasound(Voluson S10), magnetic resonance imaging (MRI) and some cases IVU were used to visualize the genital tract anomalies and any associated renal anomalies done by specialized doctor in Baghdad teaching hospital. These studies helped in confirming the diagnosis and providing detailed information on the anatomy and extent of the anomalies.

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used.

RESULTS

The study focused on participants predominantly aged 15-19 years, comprising 90% of the sample, with a mean age of 16.82 ± 3.1 years. Body mass index (BMI) analysis revealed that 78% had a normal BMI (18.5-24.9), 18% were underweight (BMI < 18.5), and 4% had a BMI of 25 or higher, resulting in a mean BMI of 20.49 ± 2.36 kg/m². Geographically, 66% resided in urban areas while 34% lived in rural settings. A family history of the condition was reported by only 10%, with 90% indicating no such history. The majority of participants (84%) were single, whereas 16% were married. Chromosomal analysis showed that 92% had XX chromosomes and 8% had XY chromosomes.

Table 1: Distribution of demographics data.

Variables		No. (%)
Age	15-19	45 (90)
	≥20	5 (10)
	Mean ±SD	16.82 ±3.1
BMI	<18.5 (kg/m^2).	9 (18)
	18.5-24.9 (kg/m^2).	39 (78)
	≥25 (kg/m^2).	2 (4)
	Mean ±SD	20.49 ±2.36
Residency	Urban	33 (66)
	Rural	17 (34)
Family history	Positive	5 (10)
	Negative	45 (90)
Marital status	Married	8 (16)
	Single	42 (84)
Chromosomes	XX	46 (92)
	XY	4 (8)

Among the study participants, imperforated hymen was the most common diagnosis, affecting 44% (n=22) of cases. Uterine agenesis with the absence of the upper two thirds of the vagina was reported in 36% (n=18) of participants. Ambiguous genitalia and high vaginal septum were observed in 6% (n=3)of each . Additionally, androgen insensitivity and cervical agenesis were present in 4% (n=2) of the participants.

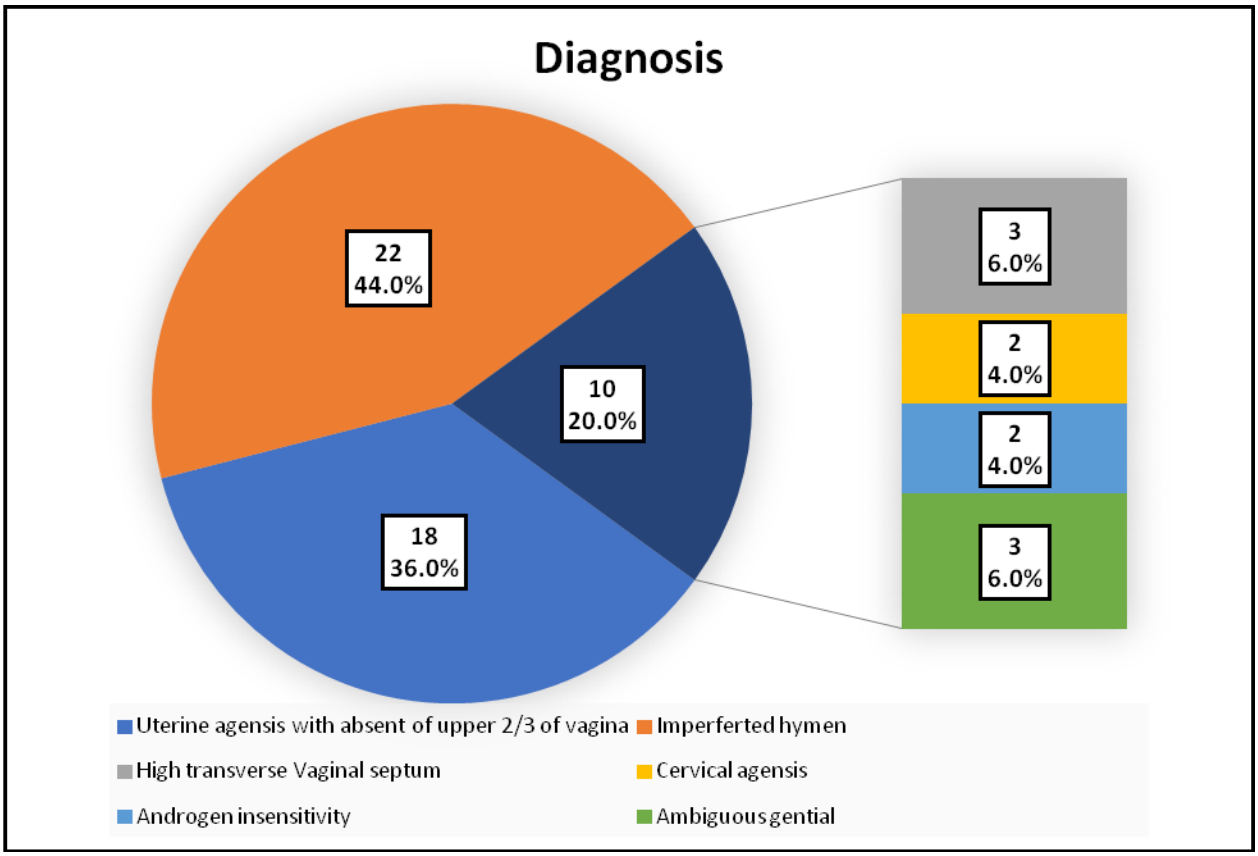

Figure 2: Distribution of cases according to diagnosis.

The biochemical analysis indicated that alkaline phosphatase (ALP) levels varied by diagnosis, with the highest mean in uterine agenesis (253.06 ± 265.47 u/l) and the lowest in cervical agenesis (72.5 ± 3.54 u/l); however, these variations were not statistically significant (p=0.105). In contrast, hepatocyte nuclear factor 1B (HNF 1B) levels showed significant variability, with the highest mean in ambiguous genitalia (1833.33 ± 737.11) and androgen insensitivity (1630 ± 1230.37), and the lowest in cervical agenesis (246.5 ± 4.95). The differences in HNF 1B levels were statistically significant (p<0.0001), indicating a strong association between certain diagnoses and HNF 1B expression.

Table 2: Distribution of ALP and HNF 1B according to diagnosis.

Diagnosis	ALP	HNF 1B
	Mean ±SD	Mean ±SD
Ambiguous genital	176 ±61.61	1833.33 ±737.11
Androgen insensitivity	137 ±29.7	1630 ±1230.37
Uterine agenesis with absent of upper 2/3 of vagina	253.06 ±265.47	924.28 ±393.65
Imperforate hymen	148.22 ±96.03	428.2 ±278.65
High transverse Vaginal septum	114 ±87.13	818 ±92.5
Cervical agenesis	72.5 ±3.54	246.5 ±4.95
P value	0.105	**<0.0001**

The study found no significant differences in alkaline phosphatase (ALP) levels across age, BMI, and chromosomal groups. Mean ALP for ages 15-19 was 161.76 ± 97.18 U/L and for those 20 and older was 390.2 ± 485.35 U/L (p=0.15). ALP levels for different BMI categories were also not significantly different: <18.5 (166.78 ± 106.68 U/L), 18.5-24.9 (187.29 ± 195.95 U/L), and ≥25 (212.5 ± 194.45 U/L) (p=0.985). Chromosomal analysis showed no significant difference between XX (187.57 ± 187.34 U/L) and XY (150.5 ± 52.72 U/L) (p=0.931). For HNF 1B, mean levels were 742.76 ± 571.95 pg/mL for ages 15-19 and 926 ± 422.07 pg/mL for those 20 and older (p=0.191). BMI categories for HNF 1B showed no significant differences as well: <18.5 (629.11 ± 339.64 pg/mL), 18.5-24.9 (818.97 ± 595.45 pg/mL), ≥25 (226 ± 24.04 pg/mL) (p=0.151). A significant difference was noted in HNF 1B levels between XX (682.48 ± 452.3 pg/mL) and XY (1665 ± 912.63 pg/mL) (p=0.017).

Table 3: Distribution of investigations according to demographics.

Variables		ALP		HNF 1B	
		Mean ±SD	P value	Mean ±SD	P value
Age group	15-19	161.76 ±97.18	0.15	742.76 ±571.95	0.191
	≥20	390.2 ±485.35		926 ±422.07	
BMI group	<18.5	166.78 ±106.68	0.985	629.11 ±339.64	0.151
	18.5-24.9	187.29 ±195.95		818.97 ±595.45	
	≥25	212.5 ±194.45		226 ±24.04	
Chromosomes	XX	187.57 ±187.34	0.931	682.48 ±452.3	**0.017**
	XY	150.5 ±52.72		1665 ±912.63	

DISCUSSION

Mutations in HNF1B gene is one of the most prevalent genetic abnormalities mainly affect kidney and urinary tract, in addition to a spectrum of extra renal manifestations that involve genital tract anomalies. The main role of HNF1B as a transcription factor required in the development of multiple organ systems (genital and urinary systems) and thus it has a significant role in embryogenesis and disease pathogenesis.[5]

This study evaluated 50 cases of genital tract abnormalities, the presentation of the cases mainly in adolescent or young adult. This dependent on the type of abnormality and its presentation which may be delayed in some HNF1B mutation-associated anomalies. Madariaga et al[5] similarly observed majority of the phenotypic expressions occur in adolescents.

The BMI observed in the current study was within normal range, although previous studies did not examined the BMI level in adolescents, El-Khairi et al[6] found that those with HNF1B mutations more prone to develop metabolic syndrome in adult life presented as obesity, and higher risk of type II diabetes.

The low percentage of positive family history (6.3%) of congenital anomalies in this study is consistent with Nakayama et al[7] study who stated that up to half of HNF1B mutations occur de novo.

This study showed that the majority of the cases were urban residency (68.8%) this result may be attributed to accessibility to healthcare facilities and referred for genetic or clinical studies. Previous studies did not show to this association.

The current study showed that imperforate hymen is the most common condition, affecting 44% of the cases (n=22). This was followed by uterine agenesis with the absence of the upper third of the vagina, found in 36% (n=18). Other diagnoses included ambiguous genitalia and high vaginal septum, each found in 6.3% of participants (n=3). Less commonly, androgen insensitivity and cervical agenesis were reported in 4.2% (n=2) each.

The most common type of anomaly in the current study was imperforate hymen, Marzuillo et al[8] found that imperforate hymen rate in general population is 0.05-0.1%. Imperforated hymen was poorly associated with HNF1B mutations (p value 0.272). Adalat et al[9] found

that imperforated hymen had no direct association with HNF1B mutations and the positive mutations in some cases are coincidental finding rather than true association.

The uterine agenesis with absence of upper two thirds of vaginal represents 37.5% of the anomalies included in the study. This anomaly was significantly associated with HNF1B mutation (p value 0.004).

Oram et al[10] investigated the role of HNF1B mutations in uterine and renal abnormalities in 108 women. The study found that 9 out of 108 women (8%) had HNF1B gene mutations. The mutation rate was significantly higher (18%) among the 50 women with combined uterine and renal abnormalities, whereas no mutations were detected in the 58 women with isolated uterine abnormalities, and suggested that this mutation is associated with combined anomalies rather that isolated uterine anomaly.

Thomson et al[11] investigated the role of HNF1B mutation and Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome which is syndrome associated with aplasia or hypoplasia of the uterus and vagina in women with a 46,XX karyotype. This result further supports the result of the current study.

Pizzo et al[12] in their literature review focusing on the etiology and genetic factors contributing to MRKH syndrome, and identified HNF1B as one of the genes potentially involved in the developmental failure of Müllerian ducts, alongside other genes such as HOXA and WNT4. While specific mutation rates for HNF1B were not detailed, the review synthesized clinical and genetic findings, emphasizing a multifactorial basis for MRKH syndrome and HNF1B mutation is one of the possible aetiologies.

The relatively low rate (6.3%) of ambiguous genitalia (other than androgen insensitivity) in this study is consistent with its rarity in general populations. Furthermore it was significantly associated with HNF1B gene mutation (P value 0.012). However, ambiguous genitalia that resulted from androgen insensitivity rather than disruptions in the normal developmental pathways of the genital tract in this case no association with HNF1B mutation. Bockenhauer et al[13] found that HNF1B mutations is more associated with structural genital tract defects rather than androgen insensitivity.

The elevated levels of HNF 1B in ambiguous genitalia and androgen insensitivity groups may point to its involvement in the pathogenesis of these conditions, particularly disorders of sex development and abnormal genital formation. These findings highlight the potential role of HNF 1B in the molecular mechanisms underlying these congenital urogenital anomalies.[14]

High vaginal septum and cervical agenesis were observed in smaller rates (6.3% and 4.2%, respectively), in line with studies reporting such anomalies as less common but significant contributors to congenital malformations. The current study showed no significant association between these abnormalities and HNF1B mutation. On the other hand, Kang et al[15] investigated the association between HNF1B mutation and vaginal septum and concluded that significant association present. The current study had small sample size leading to this non-significant association.

While HNF1B does not directly regulate ALP, mutation or dysfunction in HNF1B can lead to secondary effect that alter ALP level, often in the context of kidney, liver, or bone related issue.[16]

CONCLUSION

There is a significant association between serological HNF1B gene and certain congenital genital tract anomalies, particularly uterine agenesis and ambiguous genitalia, with elevated HNF1B levels observed in these conditions.

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