# بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / هناء محمد علي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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| **ملاحظات:**<br>.....<br>.....<br>.....<br>.....<br>..... |

# Factor VIII Level in The Potential Female Carrier mothers and its Impact on Joint Health

## Thesis

*Submitted for Partial Fulfillment of Master Degree in Pediatrics*


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**Ahmed Ebrahim Ebrahim Elkyal**

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# *List of Abbreviations*

| *abb* | *Full name* |
|---|---|
| **aPCCs** | activated PCCs |
| **CDC** | Centers for Disease Control and Prevention |
| **CFC** | clotting factor concentrate |
| **CSA** | chromogenic substrate assay |
| **CVS** | Chorionic villus sampling |
| **EACA** | epsilon amino caproic acid |
| **FVIII** | factor VIII |
| **GRE** | gradient echo |
| **H2O2** | hydrogen peroxide |
| **HA** | Hemophilia A |
| **HB** | hemophilia B |
| **HTCs** | Hemophilia Treatment Centers |
| **IL** | interleukin |
| **IU** | international unit |
| **MMPs** | matrix metalloproteinases |
| **MRI** | magnetic resonance imaging |
| **NGS** | next-generation sequencing |
| **NHS** | National Health Service |
| **NO** | nitric oxide |
| **NSAIDs** | Non-steroidal anti-inflammatory drugs |
| **OA** | osteoarthritis |

| | |
|---|---|
| **OPG** | osteoprotegerin |
| **OSA** | one-stage assay |
| **PCCs** | prothrombin complex concentrates |
| **PWH** | people with hemophilia |
| **RA** | rheumatoid arthritis |
| **RANK** | receptor activator of nuclear factor κB |
| **RANKL** | receptor activator of nuclear factor κB ligand |
| **RBC** | red blood cell. |
| **rFVIIa** | recombinant activated factor VII |
| **ROM** | range of motion |
| **S** | Significant |
| **SD** | standard deviation |
| **sEMG** | surface electromyography |
| **TNF** | tumor necrosis factor |
| **UDC** | Universal Data Collection |
| **VAS** | visual analogue scale |
| **VEGF** | vascular endothelial growth factor |
| **WFH** | world federation of hemophilia |

# INTRODUCTION

Hemophilia A; is an X-linked bleeding disorder; owing to a mutation in the genes encoding for coagulation factor VIII (FVIII), which was first reported in the medical literature during the 18th century ***(Castaman and Matino, 2019).*** Estimations based on the world federation of hemophilia (WFH)'s annual global surveys indicate that the population with hemophilia in the world is approximately 400,000 ***(Stonebraker and Bolton, 2010).***

While the characteristic phenotype in hemophilia is a life-long prolonged post traumatic bleed, Studies suggests that the low to normal FVIII activity found in hemophilia A carriers compromises hemostasis sufficiently to cause joint bleeding ***(Gilbert et al., 2014).***

Hemophilia A carriers also experience subclinical joint bleeding which could lead to structural joint damage which was demonstrated by soft tissue and osteo-chondral changes on joint MRI; in which ankle MRI ***Gilbert et al (2014).***

Early signs of synovial hypertrophy and early cartilage damage can be demonstrated by magnetic resonance imaging (MRI) of the affected joint ***(Carotti et al., 2017).***

Whether, hemophilia carriers develop subclinical joint arthropathies need to be studied.

# Aim of Work

**Primary objective:**

To assess factor VIII level in mothers of known patients of hemophilia A.

**Secondary objective:**

- To assess the frequency of arthropathy in hemophilia A potential female carrier mothers.
- To correlate the level of factor VIII with the degree of arthropathy in both potential female carrier mother.

*Chapter 1*

# Hemophilia

## Epidemiology:

Hemophilia A & B are rare inherited bleeding (XLR) disorder caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B) ***(World Federation of Hemophilia, 2018).***

Currently; Hemophilia A has been recognized in all areas of the world and in all ethnic groups. Estimates of its incidence approximate 1 in 5000 male live-births, or 1 in 10 000 live-births ***(Kadhim et al., 2019).***

Hemophilia B is less common with an incidence of 1 in 30 000 male live-births. However, hemophilia C affects about 1 in every 100,000 populations. India ranked first in number of registered patients with hemophilia (A, B, and C) in 2016, with a total number of 18,383 patients with a prevalence of 1.4/100 000 populations, followed by the United States and China. ***(Stonebraker et al., 2010)***

According to the WFH, hemophilia has an estimated frequency of approximately one in 10,000 births. Hemophilia A is more common than hemophilia B, representing 80–85% of

the total hemophilia population. According to the WFH Global Survey, there were an estimated 5,050 people with hemophilia (PWH) in Egypt in 2013 ***(World Federation of Hemophilia, 2018).***

**Etiology and Pathophysiology:**

Research has identified over 1000 mutations in the genes encoding factor VIII and IX, along arm of X-chromosome and around 30% are due to spontaneous mutation ***(Bertamino et al., 2017).***

**Types of mutations**:

Inversion mutations involving intron 22 (Inv22) and intron 1 (Inv1), account for about 45% and 2% – 5% of severe phenotype, respectively ***(Gouw et al., 2012).***

Point mutations are the most prevalent defect in 90% – 95% of patients who tested negative for inversion typing, followed by deletions in about 5% – 10%. Numerous types of previously reported HA gene mutations have been identified in exon 14. Being the largest exon in F8 gene, exon 14 provides a mutational hotspot and codes partially for two domains (A2 and A3) as well as the entire B-domain of F8 protein ***(Bastida et al., 2017).***

Recently, targeted next-generation sequencing (NGS) is utilized to sequence the whole coding region of F8 ***(Atik et al., 2020).***

**Factor VIII and IX in coagulation cascade:**

Blood coagulation is part of an important host defense mechanism termed hemostasis. Upon vessel injury, platelets adhere to macromolecules (i.e. collagen) in the sub-endothelial tissues and aggregate to form a platelet plug (primary hemostasis) ***(Periayah et al., 2017)***

Activated platelets then stimulate the local activation of plasma coagulation factors that initiate a sequential amplifying cascade, resulting in the formation of a cross-linked fibrin clot that further strengthens the platelet plug (secondary hemostasis) ***(Jain and Acharya, 2018).***