

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# **Inherited Bleeding Disorders IN Females**

# INTRODUCTION

## **Under diagnosis/ Misdiagnosis/ Late diagnosis**

- ❑ Inherited bleeding disorders in females are often under - diagnosed or misdiagnosed**
- ❑ Usually these disorders are diagnosed after a long delay**
- ❑ Diagnosed after :**
  - the development of significant iron deficiency anaemia**
  - Receiving multiple transfusions**
  - Post operative bleeding**
  - Going through many surgical procedures**

## Bleeding disorders in females: Differential Diagnosis

	Platelet disorders	Coagulation disorders	Vessel wall disorders
<b>CONGENITAL</b>	<ul style="list-style-type: none"> <li>• von Willebrand Disease</li> <li>• Bernard soulier syndrome</li> <li>• Glanzmann's Thrombasthenia</li> <li>• Storage pool disease</li> </ul>	<ul style="list-style-type: none"> <li>• Haemophilia carriers</li> <li>• Autosomal recessive coagulation disorders</li> </ul>	<ul style="list-style-type: none"> <li>• Hereditary haemorrhagic telangiactasia</li> <li>• Ehlers- Denlos Syndrome</li> </ul>
<b>ACQUIRED</b>	<ul style="list-style-type: none"> <li>• ITP</li> <li>• TTP</li> <li>• Drugs: Aspirin, NSAIDS, Antibiotics, Chemotherapy</li> <li>• Collagen diseases(SLE)</li> <li>• Leukaemias</li> <li>• MPD</li> </ul>	<ul style="list-style-type: none"> <li>• Acquired factor VIII inhibitors</li> <li>• Vitamin K deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Physical, e.g., valsalva, weight lifting</li> <li>• Infections</li> <li>• Drugs: Heparin necrosis</li> <li>• Dysproteinemias</li> <li>• Cutaneous vasculitis</li> </ul>

ITP: Idiopathic thrombocytopenic purpura ; TTP: Thrombotic thrombocytopenic purpura  
 NSAIDS: Non Steroidal anti inflammatory Drugs ; SLE: Systemic lupus erythematosus

## Type of bleeding : Differential diagnosis

### 1. MUCOSAL BLEEDING

**Defect:** Platelet plug formation or "Primary haemostasis"

**Symptoms:** Menorrhagia, epistaxis, bruising, post operative, dental, gastro- intestinal, genitourinary.

### 2. BODY CAVITY BLEEDING

**Defect:** Fibrin clot formation or "Secondary haemostasis"

**Symptoms:** Haemarthrosis, haematomas, post operative, retroperitoneal, central nervous system

### 3. PETECHIAE, ECHYMOSIS, PURPURA

**Defect:** Vessel wall abnormality

**Symptoms:** Telangiectasia, gravity -dependent lesions, palpable Vs non - palpable

**OBJECTIVE**

# An Over view

**An overview of the common inherited bleeding disorders in females focusing on their:**

- **Clinical manifestations**
- **Complications**
- **Diagnosis ,**
- **Treatment options**
- **Hindrances in their management**

**PATIENTS  
&  
METHODS**

- ❑ Non - interventional descriptive study**
- ❑ Females with inherited bleeding disorders presenting to Haemophilia Patients Welfare Society, Rawalpindi/Islamabad chapter and District Head Quarters Hospital Rawalpindi were analyzed.**
- ❑ Demographic data, presenting episodes, diagnostic evaluation and treatment received were recorded**

- ❑**Diagnosis was established on the basis of Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) , Thrombin Time (TT), Bleeding Time (BT), Clotting Time (CT), factor level estimation ,platelet count , platelet aggregation studies and examination of peripheral smear.
- ❑**Mixing studies were performed by using aged serum (24 hours old serum kept at 37 ° C) and adsorbed plasma (normal plasma adsorbed by barium sulphate).
- ❑**Factor levels were estimated by using commercially available deficient plasmas
- ❑**Platelet aggregation studies were performed by collecting 10 ml of blood in sodium citrate. Platelet rich plasma (PRP) was prepared by centrifuging the samples at 250 xg and 1500 xg respectively for ten minutes. The aggregation pattern was studied against different agonists ( ADP, Epinephrine, Ristocetin, Collagen)

# RESULTS

## Distribution of inherited bleeding disorders in females

❑ Total number of patients with inherited bleeding disorders = 343

❑ Female patients with inherited bleeding disorders = 57/343 (16.78%)

Disease	Number of Patients(%)
von Willebrand Disease	29/57 (50.87%)
Glanzman's Thrombasthenia	9/57 ( 15.78%)
Factor V Deficiency	7/57 (12.28%)
Factor X Deficiency	4/57 ( 7.01%)
Factor XIII Deficiency	4/57 ( 7.01%)
Bernard Soulier Syndrome	3/57 ( 5.26%)
Factor XI Deficiency	1/57 ( 1.75%)

## Inherited bleeding disorders in females: Age distribution

Age	Number of patients (%)
Less than 5 years	9/57 ( 15.78%)
6 - 15 years	39/ 57 (68.41%)
16 - 25 years	5 / 57 (8.77%)
26 - 35 years	2 / 57 ( 3.5%)
36 - 45 years	1 / 57 (1.75%)
46 - 55 years	1 / 57 ( 1.75%)

## Inherited bleeding disorders in females: Bleeding episodes

<b>Spontaneous</b>	<b>324 / 341 (95.01%)</b>
<b>Injury associated</b>	<b>17 / 341 (4.99%)</b>

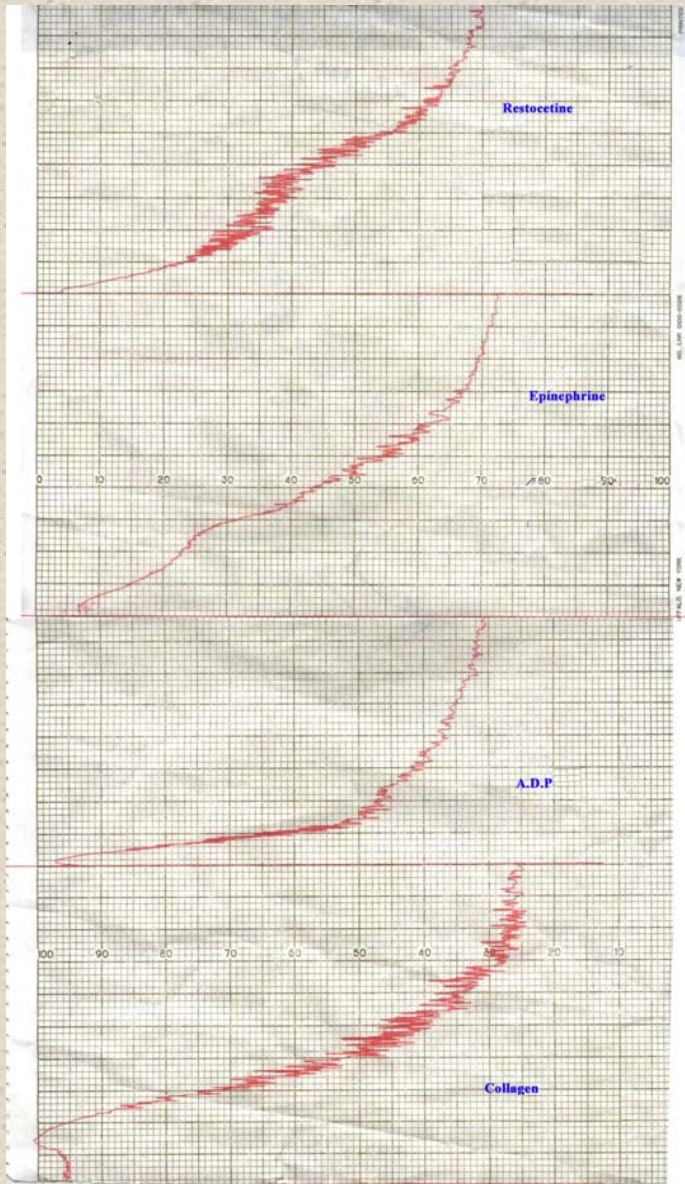
## Inherited bleeding disorders in females : Bleeding episodes

<b>Episode</b>	<b>Number of episodes (%)</b>
<b>Menorrhagia</b>	<b>160 / 341 ( 46.92%)</b>
<b>Epistaxis</b>	<b>60 / 341 ( 17.59%)</b>
<b>Gum bleed</b>	<b>40 / 341 ( 11.73%)</b>
<b>Dental bleed</b>	<b>30 / 341 ( 8.79%)</b>
<b>Bruising</b>	<b>20 / 341 ( 5.86%)</b>
<b>Joint bleed</b>	<b>20 / 341 ( 5.86%)</b>
<b>Umbilical cord bleed</b>	<b>4 / 341 ( 1.17%)</b>
<b>Haemorrhagic ovarian cysts</b>	<b>4 / 341 ( 1.17%)</b>
<b>CNS bleed</b>	<b>2 / 341 ( 0.58%)</b>
<b>Postpartum bleed</b>	<b>1 / 341 ( 0.291 %)</b>

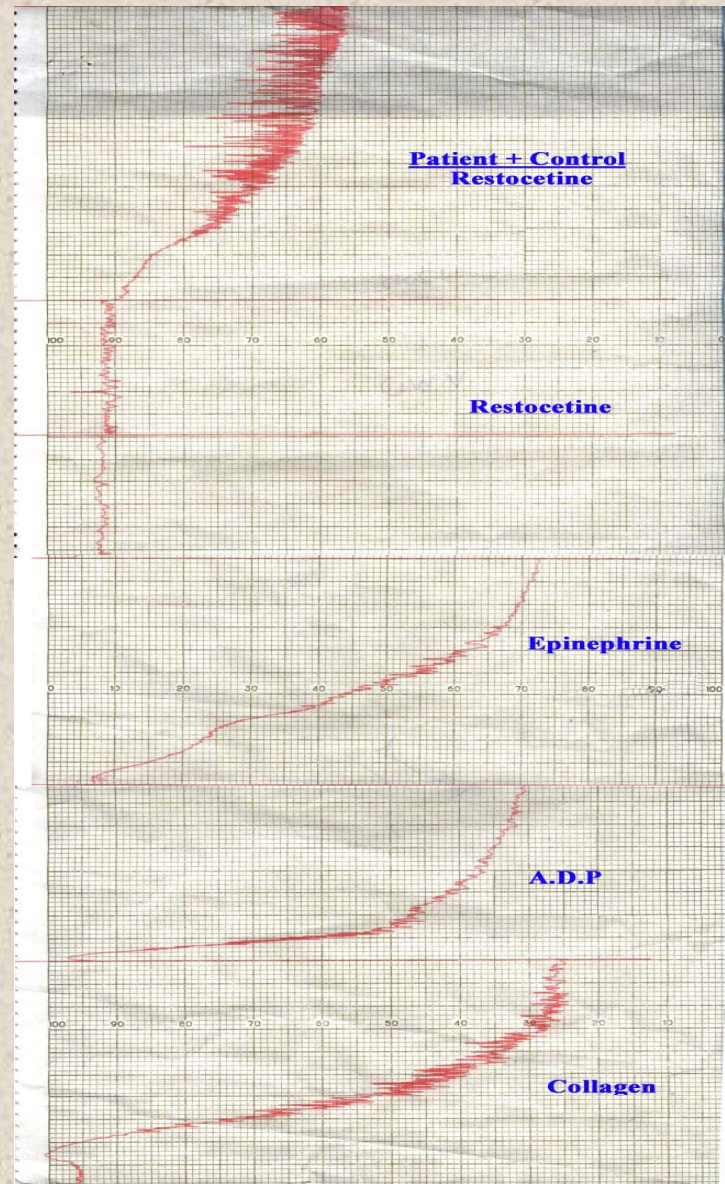
## Inherited bleeding disorders in females: Platelet studies

	von Willebrand Disease	Glanzmann's Thrombasthenia	Bernard Soulier Syndrome
Platelet count	Normal	Normal	Decreased
Platelet size	Normal	Normal	Large
Aggregation with ADP	Normal	Absent	Normal
Aggregation with Collagen	Normal	Absent	Normal
Aggregation with Ristocetin	Absent	Normal	Absent
Aggregation with Epinephrine	Normal	Absent	Normal

# von Willebrand disease: Platelet function studies

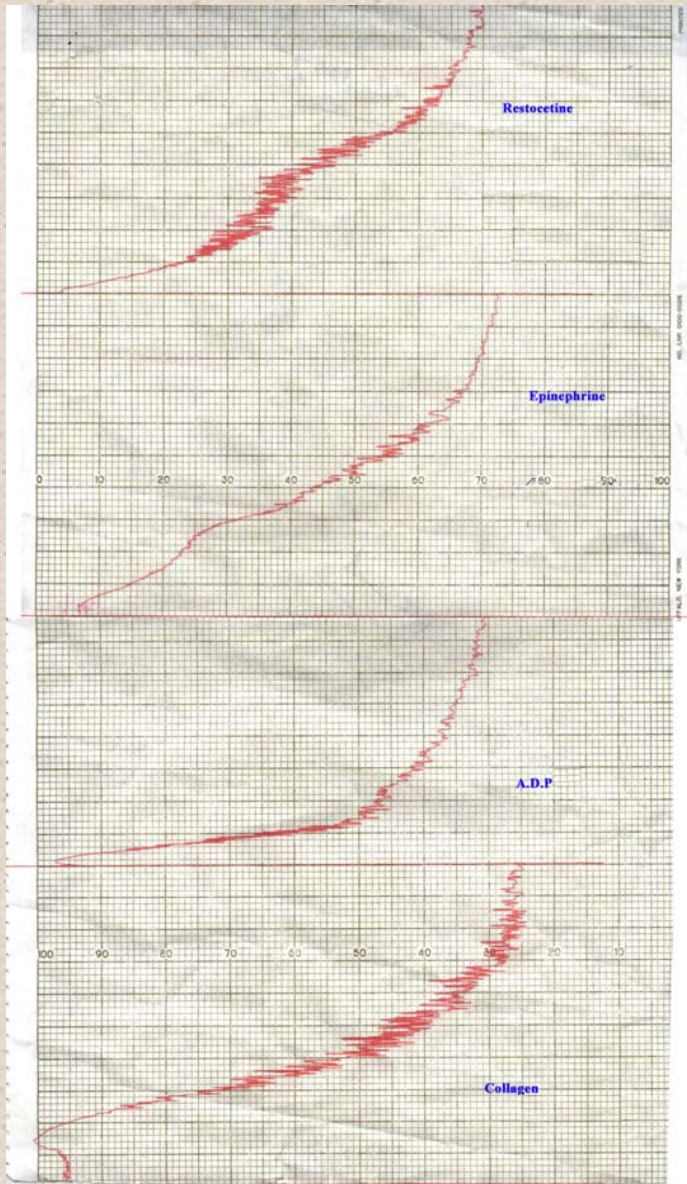


Normal control

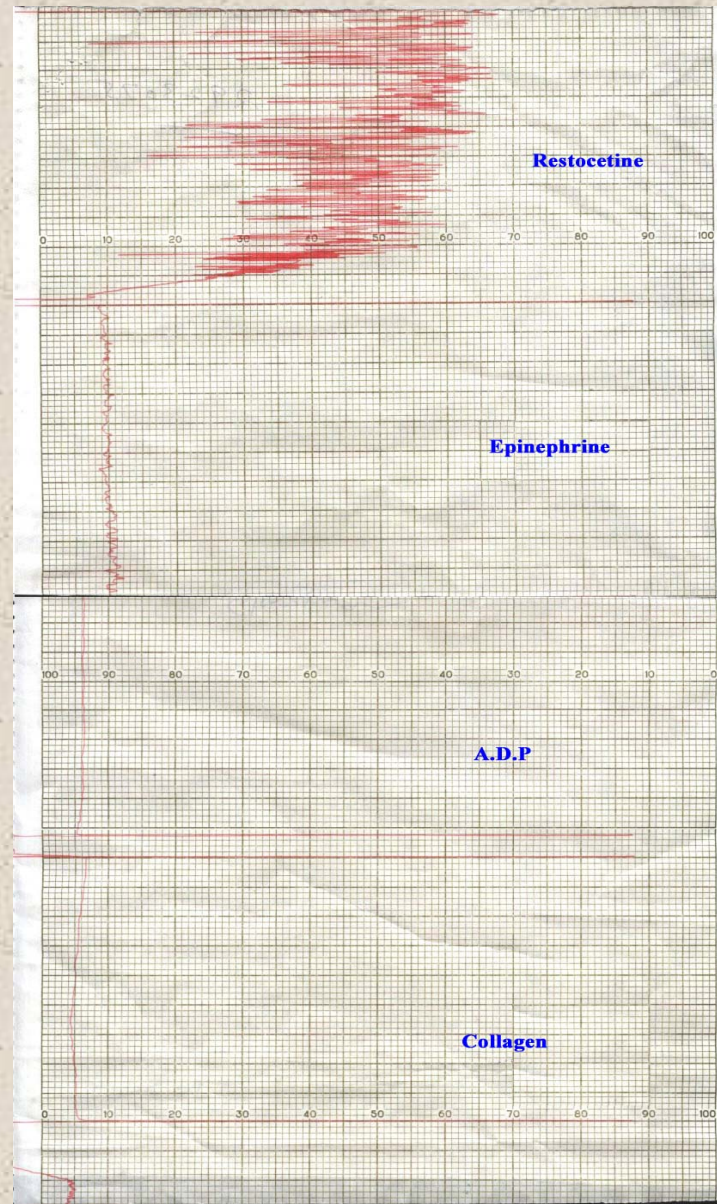


von Willebrand disease

# Glanzman's Thrombasthenia : Platelet function studies



Normal control



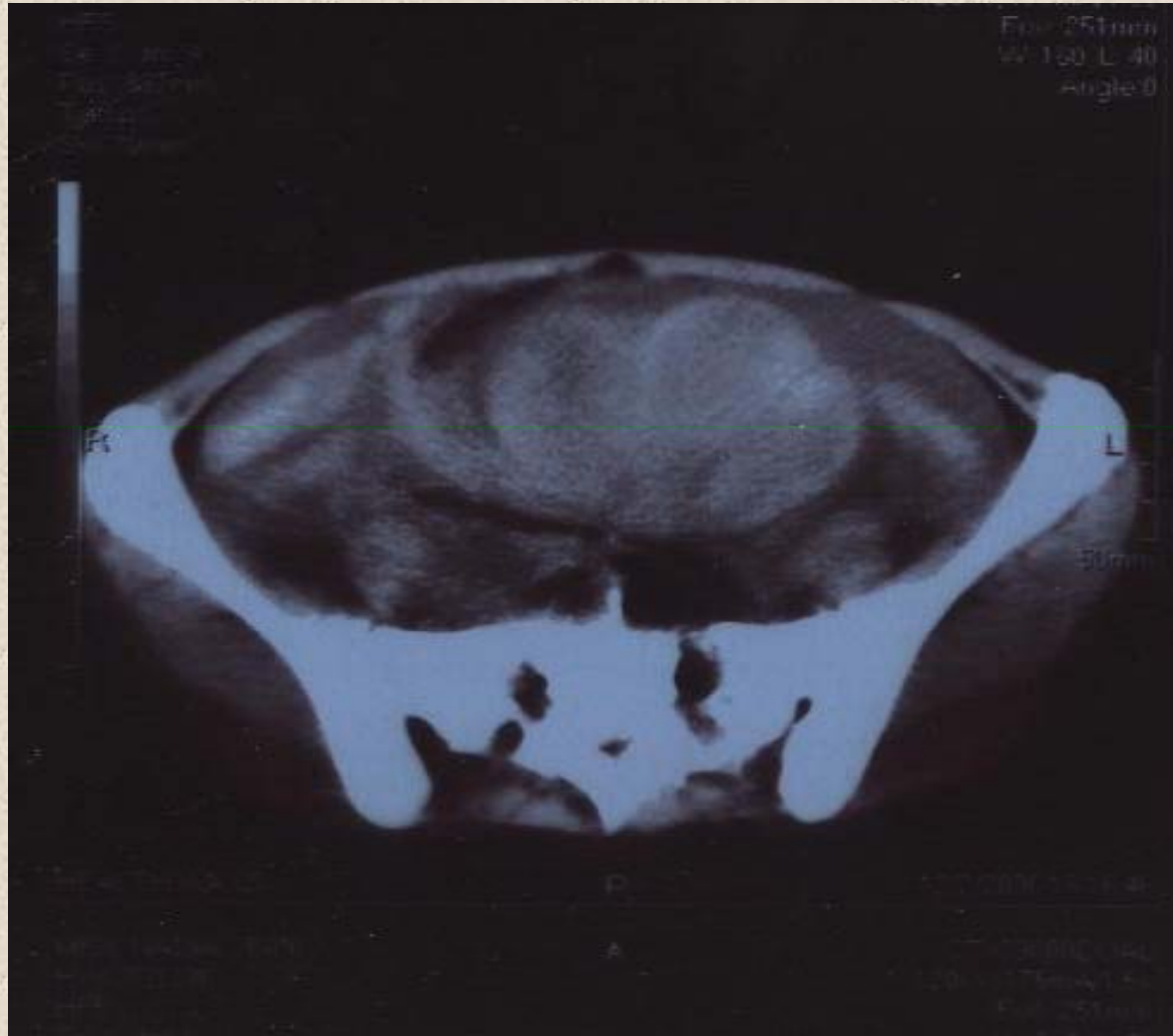
Glanzman's Thrombasthenia

## Inherited bleeding disorder in females: Haemorrhagic Ovarian cyst



Ultrasound Abdomen & Pelvis in a case of Haemorrhagic Ovarian Cyst showing a solid mass in pelvis

**Inherited bleeding disorder in females: Haemorrhagic Ovarian cyst**



**CT Scan Pelvis: Showing large mixed density hyper dense mass in mid abdomen/ pelvis**

## Inherited bleeding disorders in females: treatment received\*

Treatment	Number of episodes
Tranexmic Acid	80 / 96
Fresh Frozen Plasma	40 / 96
Cryoprecipitate	10 / 96
Platelet's concentrates	30 / 96
Kaote	5 / 96
DDAVP	20 / 96
Hormonal therapy	37 / 96
Recombinant Factor VII	2 / 96
Dilatation and Curettage	10 / 96
Leparotamies	5/96
Hysterectomies	3 /96

\*Record of 96 episodes

# DISCUSSION

## **Congenital Bleeding Disorders in Females: Compounding of the problems**

- ❑ Females with inherited bleeding disorders have clinical manifestations very much akin to their male counterparts with the same diagnosis. Additionally these females can have clinical manifestations which are very much specific to female genital tract**
- ❑ While women with inherited bleeding disorders are at risk for the same obstetrical and gynaecological problems that affect all women, they appear to be disproportionately affected by conditions that manifest with bleeding**

## von Willebrand Disease

- ❑ World wide it is considered as the commonest inherited bleeding disorder
- ❑ Approximately 84% of women with vWD reported menorrhagia , the highest prevalence for any bleeding symptom .
- ❑ Three main types :
  - **Type 1 vWD**: Quantitative defect of vWF
  - **Type 2 vWD(2A,2B,2M,2N)**: Qualitative defect of vWF
  - **Type 3**: Near or complete absence of vWF
- ❑ The prevalence of different subtypes of vWD is not known in our set up, which is essential for proper management of these cases.

## von Willebrand Disease ..... contd

❑ In our set up majority of cases of vWD are of severe disease

**BUT**

World wide Type 1 ( the milder form) is more common

❑ It show :

- We are under diagnosing milder forms of vWD
- Consanguineous marriages may be responsible for severe forms (Type -3 and 2N)

## Haemophilia Carriers

- ❑ **British Queen Victoria (1819 – 1901) was a known haemophilia carrier**
  
- ❑ **Symptomatic carriers with mild disease**
  
- ❑ **Carrier detection**
  - **Daughters of men with haemophilia carriers are obligate carriers**
  - **Difficult area: carrier status in an extended haemophilia family:**
    - **Woman with an effected maternal uncle may or may not be a carrier**
    - **A pregnant woman with a vague history of a bleeding disorder in a distant relative**

## Platelet function defects

### ❑ Common types:

1. **Glanzmann's Thrombasthenia: Defective aggregation**
2. **Bernard Soulier Syndrome: Defective clot initiation**
3. **Storage pool defect: Defective extensive phase of clot formation**

❑ Most platelet defects mimic the symptoms of vWD with prolonged mucocutaneous bleeding

❑ Many of these disorders share common treatments

❑ More common in areas where consanguinity is more prevalent or in small, geographically or ethnically isolated communities

## **Autosomal Recessive Congenital Bleeding Defects in Females**

- ❑ Can affect both males and females**
- ❑ More common in countries where consanguineous marriages are more frequent**
- ❑ All these are associated with menorrhagia, recurrent abortions, haemorrhagic ovarian cysts, post partum haemorrhages and many other complications related with female reproductive system**

## **Gynaecologic & Obstetric Problems in Females with Inherited Bleeding Disorders**

- **Menorrhagia/ Metorrhagia**
- **Dysmenorrhea & mid cycle pain**
- **Post partum haemorrhage**
- **Haemorrhagic ovarian cysts**
- **Conception/ fertility problems**

## **Menorrhagia - the commonest presentation**

- ❑ Menorrhagia: Heavy menstrual bleeding**
- ❑ Metorrhagia: Irregular menstrual bleeding**
- ❑ Menorrhagia is the commonest presentation in females with inherited bleeding disorders**
- ❑ Estimates suggest that 10 to 20% of women with menorrhagia have an underlying bleeding disorder**
- ❑ About 80% of women with inherited bleeding disorders suffer from menorrhagia**

## Menorrhagia & screening for inherited bleeding disorders

- ❑ Should be ruled out in all females who present de novo with bruising and bleeding/menorrhagia.
- ❑ Should be ruled out in all females who present with Menorrhagia typically at menarche, in contrast to acquired causes of menorrhagia which may cause late or in accordance with underlying pathology

## **Post partum Haemorrhage - A serious life threatening problem**

**❑ Pregnancy causes a rise in all plasma clotting factors, except factor IX**

**BUT**

**❑ Following child birth there is a rapid fall which may lead to post partum haemorrhage**

## Haemorrhagic Ovarian Cysts - An abdominal Emergency

- ❑ These are due to excessive bleeding into the corpus luteum at the time of ovulation
- ❑ Rupture of these cysts can result in:
  - Haemoperitonium
  - Production of excessive fibrin which can lead to formation of pelvic adhesions, occlusion of fallopian tubes and destruction of ovarian tissue

## Conception/ Fertility problems

- ❑ **Hindrances in conception / Fertility:**
  - **Hormonal therapy or contraceptive pills**
  - **Pain and bleeding during intercourse**
  - **Impact on embryo implantation**

## Confounding variables in Lab Diagnosis

- ❑ Time of testing in a woman's cycle is an important confounding factor
- ❑ Estrogen level can interfere in the estimations
- ❑ Proper time for testing: First four days of a woman's menstrual cycle.
- ❑ Hormone therapy and contraceptive pills need to be stopped before lab testing

## **Inherited bleeding disorders in Females – Medical Treatment Options**

- **Antifibrinolytics (Tranexmic Acid)**
- **Hormone therapy**
- **Platelet transfusions**
- **Desmopressin Acetate**
- **Fresh Frozen Plasma/ Cryoprecipitate**
- **Factor Concentrates**
- **Iron Supplementation**
- **Non Steroidal Anti Inflammatory (NSAIDS)**
- **Recombinant Factor VII**

## Inherited Bleeding Disorders in Females - Surgical Treatment Options

- Endometrial ablation
- Levonorgestrel - releasing intrauterine system (Mirena Coil)
- Oophorectomy
- Dilatation & Curettage
- Hysterectomy
- Management of Pregnancy
- Bone Marrow Transplantation

## **Management Options - Advantages / Disadvantages**

**Tranexmic Acid** is the first line and most frequently used medication

**Contraceptive pills** - Effective in raising all clotting factors, except Factor IX

**Platelet Transfusions** - Platelet refractiness after long term administration

**Factor Concentrates** - Recombinently engineered factor VIII concentrates are VWF deficient

**Recombinant Factor VII** - Short half life; high cost ;  
contraindicated in DIC

**Bone Marrow Transplantation:** Showed good results in platelet function defects

## Management Options - Advantages / Disadvantages

Any major or Minor Surgical procedure in patients with inherited bleeding disorders should not be performed without deficient factor coverage

Dilatation & Curettage - May not be effective as it removes any existing platelet plugs and fibrin clots from the uterus

Hysterectomy - Consider when all other measures fail

Management of Pregnancy

# Conclusions

## CONCLUSIONS

### Delay in diagnosis and improper treatment

- Delay in diagnosis and failure to get proper management translate into an irreparable damage to patients well being.

## CONCLUSIONS

### Impaired quality of life and risk of unindicated surgeries

- ❑ Bleeding manifestations severely affect quality of life of the women with inherited bleeding disorders, leading to :
  - Limitation in the performance of day to day chores.
  - Loss of faith on medical profession after being told for years their problems were not real ,
  - Change in career
  - Constant fatigue due to iron deficiency
  - Painful menstruation or coitus
  - Feeling of embarrassment
  - Undue endometrial biopsies and hysterectomies

## CONCLUSIONS

### Failure to get benefit from available treatment modalities

- Failure to investigate the women with inherited bleeding disorders limit the potential benefits of different therapies like, desmopressin (DDAVP), tranexmic acid, FFP and cryoprecipitate .
- A proper management approach is usually rewarded with an overall change in the patient's personality.

## CONCLUSIONS

### **Anxiety associated with diagnosis**

- ❑ While females with severe manifestations needs proper recognition and management ; but in asymptomatic cases, patients with mild diseases or carriers , the benefits of diagnosis must be weighed against the stigma and undue anxiety associated with it.

## CONCLUSIONS

**To raise understanding of these disorders**

- ❑ **An awareness about the intricacies of these disorders will hopefully result in improved services and a better quality of life for these women, who are suffering from protean manifestations**