

# IAMANEH EGYPT 2006



# Viral hepatitis with pregnancy



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**Acute and chronic necroinflammatory liver disease caused by hepatotropic virus infection continues to be a major world health problem .**

- Approx. 5% of the worlds population has chronic HBV ( WHO 1975).**
- In the States, end stage liver disease caused by chronic HCV is the most common indication for liver transplantation (Detre et al 1996)**

# Viral hepatitis often affects women of child bearing age and their infants

- In areas where Chronic HBV is prevalent , most new cases are the result of perinatal and neonatal infection .
- HAV infection in these regions also occurs during childhood or in young adults .
- HCV is often acquired by teenagers and young adults as a result of parenteral exposure to blood or blood products.

So all obstetricians and gynecologists are likely to encounter patients with viral hepatitis specially those working in areas where this is an endemic disease .

- They must be prepared to deal with issues related to acute and chronic infection , sexual and vertical transmission ,as well as screening and treatment

# Hepatotropic viruses

	A	B	C	D	E
Family	Picornia	Hepadna	Flavi	Delta	Un Certain
Genome	RNA 27 nm	DNA 42 nm	RNA 55 nm	RNA 35 nm	RNA 27 nm
Spread	F- O	Parenteral Sexual Vertical	Parenteral Sexual ? Vertical ?	Parenteral Sexual Vertical	F- O
Fulminant	1%	1%	Rare or no	<5%	Preg.
Chronic	No	5%	85%	50%	No

Other causes of viral hepatitis are CMV, HSV, EBV, VZV  
 (All are of the Herpes group)

# Hepatitis A Virus

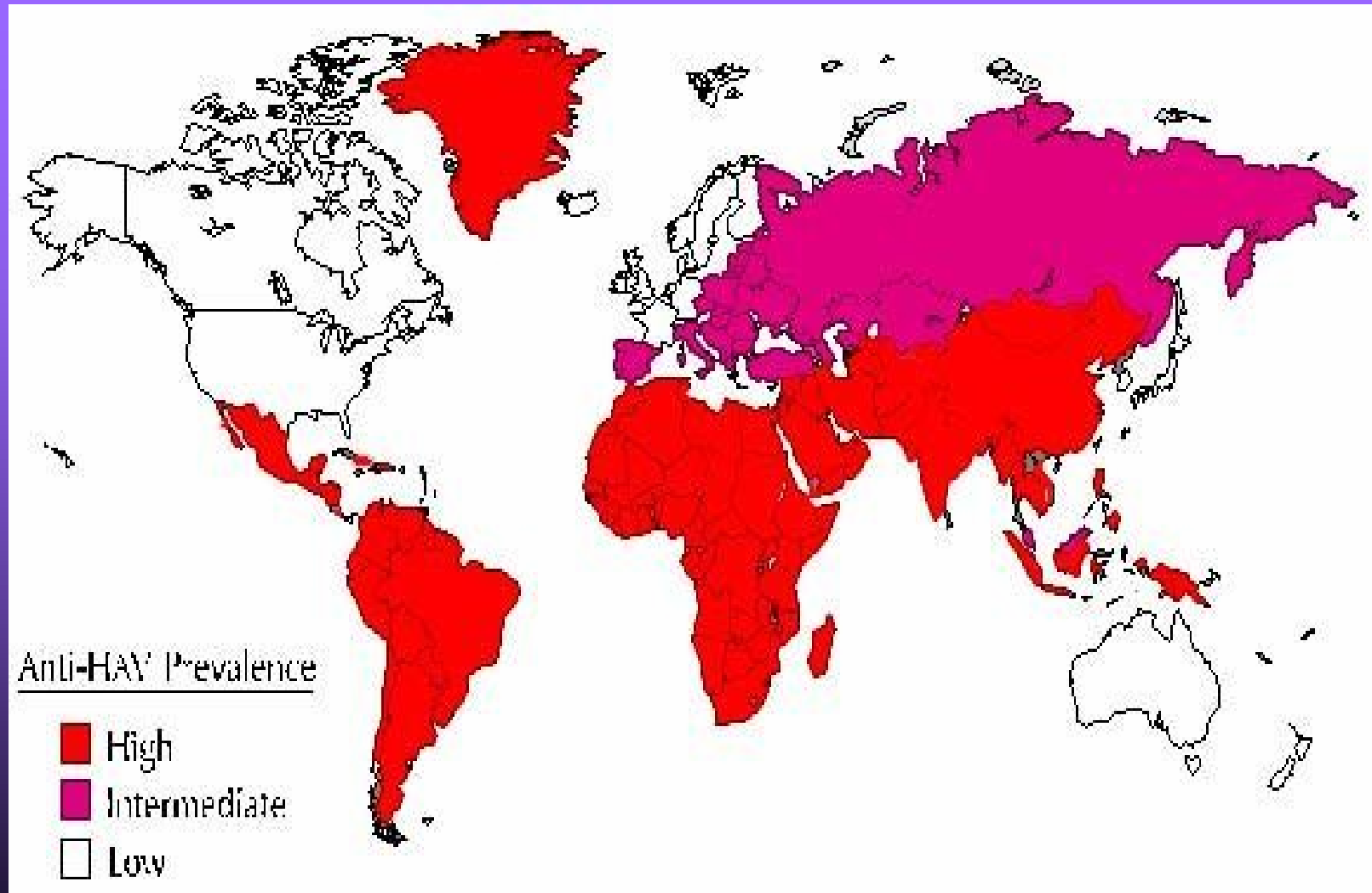
Single stranded RNA Virus -27nm .

Picornavirus group : this group is so diverse more than 200 types and also oldest known viruses (Temple record 1400BC ).

HAV has seven genotypes but only one serotype : ie IgG antibody confers immunity to infection with any genotype .

HAV replicates in the hepatocyte cytoplasm .Virus is not cytopathic , liver cell injury is caused by the host immune response

# Endemic areas for HAV



# Hepatitis A

- **Incubation period=15-50 days**
- **Fecal to oral transmission : horizontal transmission and virus is excreted in stools mainly**
- **Symptomatic cases : in 5%of children and 80% of infected adults : Anorexia –Nausea-Vomiting-Fever - Jaundice –hepatic tenderness-dark urine**
- **Asymptomatic : especially in endemic areas and children**
- **Diagnosis : serum ALT-AST –Bilirubin**
- **AntiHAV IgM 100%- (25-30d persist for60 d)**
- **AntiHAVIgG 35-40d and remain indefinitely meaning life long immunity**
- **Mostly self limited disease -<0.5% fulminant hepatitis**

# Hepatitis A Virus

**HAV vaccine : it is formalin inactivated virus : Havrix (SmithKline) and Vaqta (Merck) .**

single dose =protection after 15days . Booster may be needed after 6 month

**Passive immunization : pooled human serum Ig containing HAVIgG.**

**If Given 3-6 months before or within 2 weeks of exposure it attenuates or prevents hepatitis in 85-95% .**

**Both are recommended for travelers to endemic areas .**

**Both Ig and the vaccine are safe for use in pregnant women**

# Hepatitis A

- **HAV has the same course during pregnancy as in the non pregnant patient.**
- **Chronic carrier doesn't exist**
- **Intrauterine and perinatal mat-fetal transmission was reported, ,however it is not associated with fetal loss or developmental abnormalities**
- **Mothers with HAV have no restrictions about breast feeding**
- **Infant of acutely infected mother should take Ig as passive immunisation to prevent horizontal infection**

# Hepatitis E Virus

**Single stranded RNA Virus -32-34nm .**

**Genus Unknown.**

**HEV has 3 genotypes but only one serotype :ie IgG antibody confers immunity to infection with any genotype .**

**HAV replicates in the hepatocyte cytoplasm .Virus is not cytopathic , liver cell injury is caused by the host immune response**

# Hepatitis E Virus

## Diagnosis:

positive serum test for anti HEV IgM, and IgG, .

Western blot assays

Enzyme immunoassays

Both developed to detect anti HEV ,They are more sensitive (80-100%) than Fluorescent antibody blocking assay .

# Hepatitis E

- HEV is a disease of 3<sup>rd</sup> world regions occurring in large epidemics
- Incubation period=15-65 days
- Feco- oral transmission : horizontal transmission
- Symptomatic cases : mostly childbearing age and clinical illness develops in 70-80% of infected persons ranging from mild to severe.
- Fulminant in less than 1% of patients

# Hepatitis E with pregnancy

HEV infection is fulminant in :

1%= non pregnant

20% in Pregnant women

Fatality rate of HEV is :

0.5-4% in non pregnant

In pregnant women it is :

1.5% in the 1<sup>st</sup> trimester

8.5% in the 2<sup>nd</sup> trimester

21% in the 3<sup>rd</sup> trimester . ???

Reason for this is obscure

# Hepatitis E with pregnancy

**Infection in the 3<sup>rd</sup> trimester carries increased risk for fetal complications .**

**Death of the neonate is much more common than it is from other types of viral hepatitis**

**HEV infection is never chronic .**

# Hepatitis E

- **Prevention depends on improvements in sanitation and protection of the purity of water supplies .**
- **In endemic areas: boiling water ,avoid ice, unpeeled ,uncooked fruits & vegetables may provide protection**
- **pregnant women should not travel to endemic or to areas with known cases of HEV.**

# Hepatitis E

- Immunoprophylaxis is not available or not effective *Khuroo et al 1995*
- Treatment of infection remains supportive
- Fulminant hepatitis by HEV may resemble liver failure in acute fatty liver of pregnancy and in HELLP syndrome so it should be considered in pregnant women in endemic areas who develop fulminant hepatitis

# Hepatitis B Virus

It is a DNA Virus – intact virus is called Dane particle .

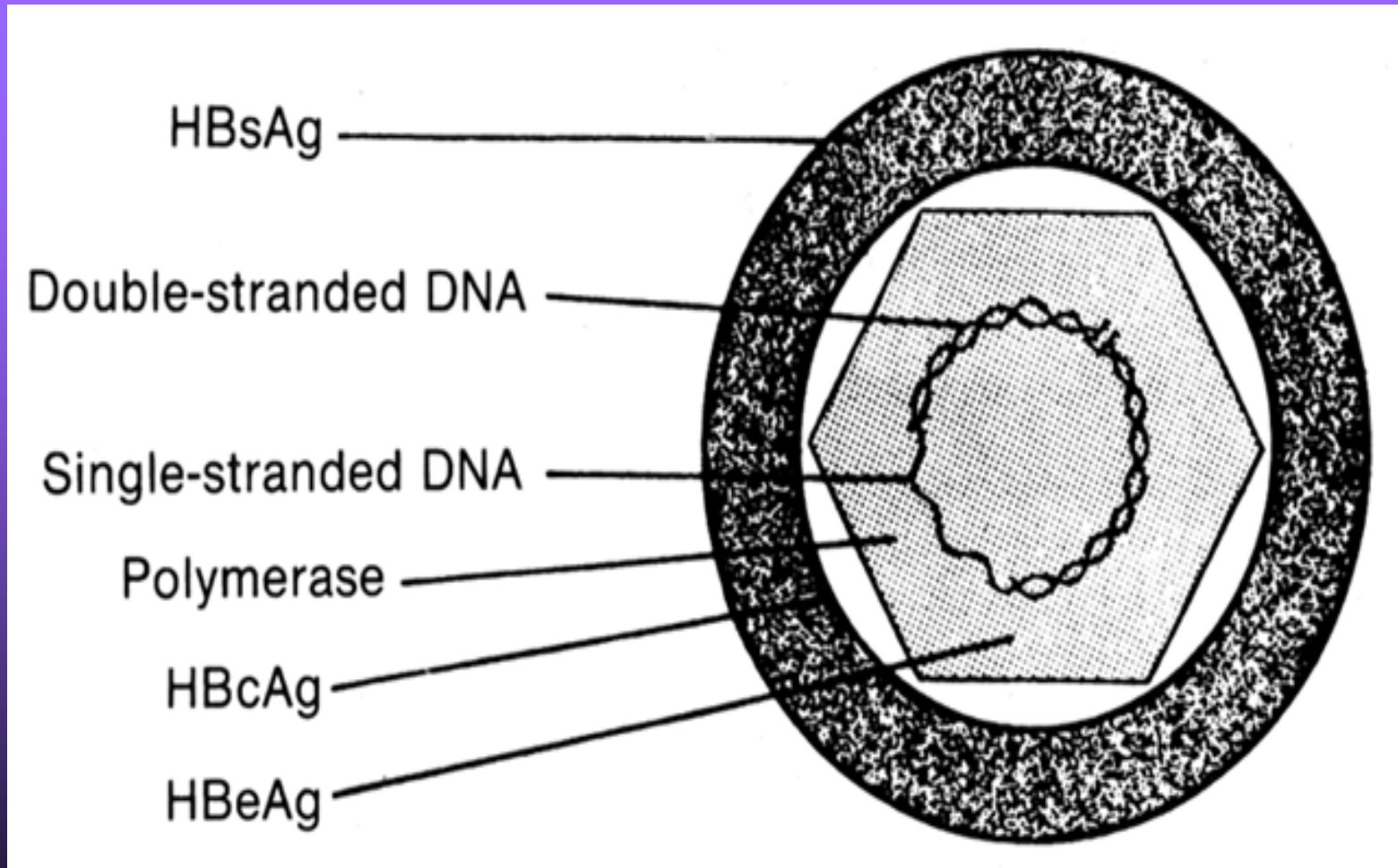
Family: Hepadnavirus type 1

HBV has 5 genotypes but only one serotype :  
ie IgG antibody to the HBV surface antigen confers immunity to infection with any genotype of HBV.

HBV replicates in the hepatocyte cytoplasm  
.Virus is not cytopathic , liver cell injury is caused by the host immune response

Acute and chronic HBV infection are diagnosed by a positive serum HBV surface antigen test

# Diagrammatic structure of the HBV



# (HBV) endemic areas over the world



**Asia, China, Philippine are highly endemic area with a prevalence rate > 8%**

# Hepatitis B Virus

Modes of transmission are

Both horizontal through parental (non sexual and sexual )exposure to blood , blood products ,semen ,vaginal secretions and saliva and vertical from mother to infant

Incubation period is 40-150 days

Illness may be :

- Acute and subclinical in 70% of adult infections
- Acute and symptomatic in 30% of adult infection
- Chronic in < 5% of acute adult infection
- Fulminant in < 1% of acute adult infection

Chronic HBV infection predisposes affected individuals to develop cirrhosis ,and hepatocellular carcinoma

# Risk factors for HBV

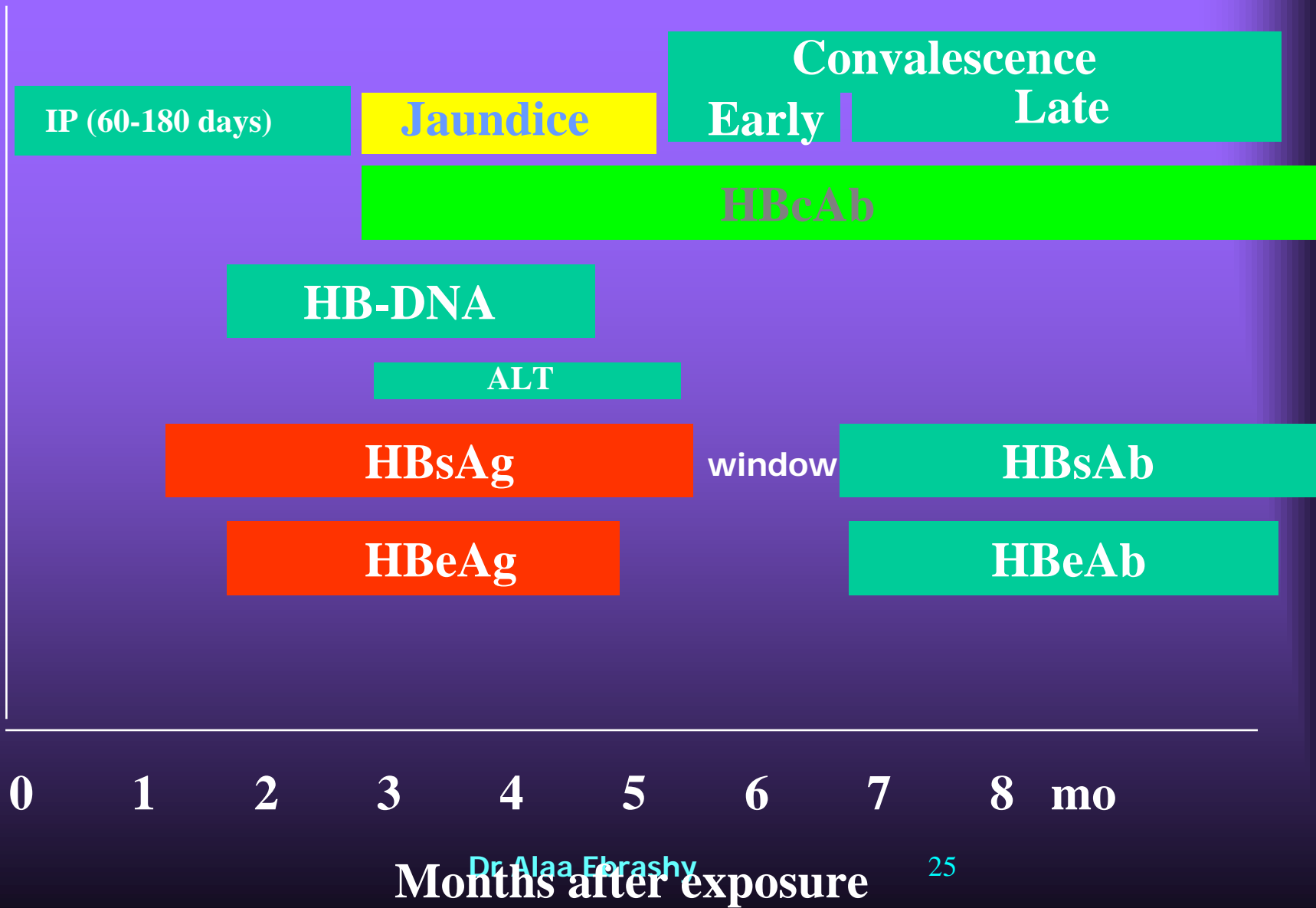
- Blood, blood product recipient
- Hospital workers
- Drug addicts
- Homosexual
- Infants of carrier mothers
- Dental surgery
- Tattooing
- Organ transplant recipient

# Clinical aspect of HBV

- **Acute phase:**
  - Manifestations range from subclinical hepatitis to anicteric hepatitis, icteric hepatitis, and fulminant hepatitis
- **Chronic phase:**
  - Manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatic cancer.

# Infection

## Course of HBV



# Serodiagnosis of HBV

	HBsAg	HBcAb	HBsAb
I.p	+	-	-
Acute	+	IgM	-
Window	-	IgM	-
Chronic	+	IgG	-
Immune	-	IgG	+
Vaccination	-	-	+

**Vaccine-related immunity can be distinguished from natural immunity by the absence of HBcAb in the serum of vaccinated patients as HBV vaccine contain only HBsAg**

# Hepatitis B serodiagnosis

- **Patients with serum HBe antigen indicates active viral replication in acute or chronic infection**
- **Whilst patients with serum HBe antibodies denote recovering from acute HBV infection or patients with chronic HBV infection but without active viral replication**

# Fate of HBV infection

## Neonatal hepatitis

## Adult hepatitis

Acute infection

Clinical or subclinical

Acute infection

Clinical or subclinical

2%



90%



Chronic infection

Chronic infection

98%



10%



# Chronic hepatitis B

	Chronic active	Chronic persistent
HBsAg	+	+
HBeAg	+	-
HB-DNA	+	+
Clinically	+++	+
Biopsy	Periportal hepatitis Loss of architecture Necrosis Piecemeal Bridging	Portal hepatitis Preserved architecture No necrosis

# Vertical transmission of HBV



**Mother with HBsAg positive (chronic)  
Transmission is less  
with HBeAg negativity**



**Mother with Acute hepatitis  
Transmission is more  
in late pregnancy**

# Risk of vertical transmission of HBV

HbsAg	HbeAg	HbeAb	Risk percent
+	+	-	57
+	-	-	20
+	-	+	11

Unlike HIV, caesarean section is not recommended to prevent vertical transmission as the vaccine is efficient.

Vertical transmission of HBV can be repeated in subsequent pregnancy as protecting antibody develops late.

# Hepatitis B with pregnancy

- Prevention of vertical transmission entails the diagnosis of acute or chronic HBV infection in pregnant women
- This justifies mandatory serum HBsAG testing for all pregnant women (*ACOG Technical Bulletin 1992*)
- Infants of potentially infected mothers are treated with HBV Immunoglobulin at delivery .

# Hepatitis B with pregnancy

- **Universal vaccination of children before age 2 months was recommended by the US public health service in 1992 and elicits an antibody response in 95% of individuals .**
- **Women with chronic HBV infection should be referred for appropriate evaluation and care after pregnancy**

## Immunoprophylaxis regimens to prevent HBV transmission

HBsAg	HbeAg	HbsAb	Interpretation	Action
-ve	-ve	-ve	Susceptible	Engerix-B
-ve	-ve	+ve	Immune	Nil
+ve	+ve	-ve	Chronic disease	Neonate protection
+ve	-ve	-ve	Carrier	Neonate protection

**Engerix-B doses**

**0, 1, 6 months**

**For young (10 µg /3 doses ) For adult (20 µg / 3 doses)**

## Recommended HBV immunoprophylaxis for neonates

HBsAg status of mother	Vaccine HBVV and HBIG	age
HBsAg-positive mothers	<b>HBIG 0.5ML IM</b> <b>HBVV 1<sup>st</sup> dose</b> <b>HBVV 2<sup>nd</sup> dose</b> <b>HBVV 3<sup>rd</sup> 1<sup>st</sup> dose</b>	Birth age-12hours Birth age-12hours 1 month 6 month
HBsAg-unknown mothers	HBIG 0.5ml im HBVV 1 <sup>st</sup> dose HBVV 2 <sup>nd</sup> dose HBVV 3 <sup>rd</sup> dose	Birth age-12hours Birth age-12hours 1 month 6 month
HBsAg-negative mothers	HBVV 1 <sup>st</sup> dose HBVV 2 <sup>nd</sup> dose HBVV 3 <sup>rd</sup> dose	Before discharge 1 month 6 month

# Indication for HBV vaccination

- Health care workers
- Blood or blood product recipient
- Contact with HBV carrier
- Neonate of an infected mother
- Needle prick of surgeon

Pregnancy is not a contraindication for active, passive immunization or both.

The role is active immunization pre-exposure and both active and passive immunization post-exposure

# Hepatitis C Virus

Single stranded RNA Virus .Flavivirus group  
Six major genotypes with 50 subtypes .

Unknown number of serotypes .within a single infected person ,HCV is present in the form of multiple quasi species : viral particles with very similar but heterogeneous RNA sequences that develop as a result of mutation during viral replication .

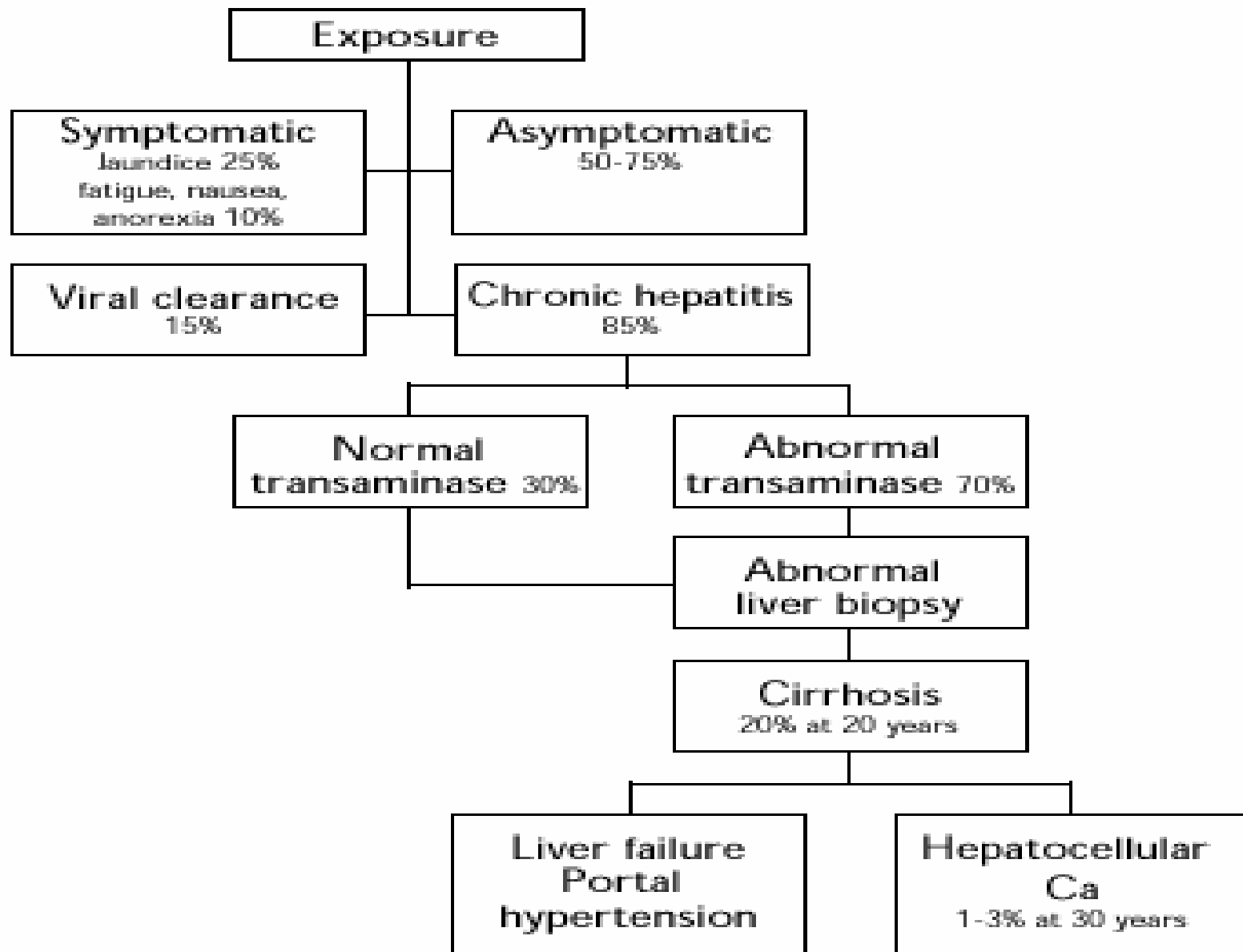
Positive serum test for HCV Antibodies indicates active infection in most cases

HCV replicates in the hepatocyte cytoplasm .Virus is not cytopathic , liver cell injury is caused by the host immune response

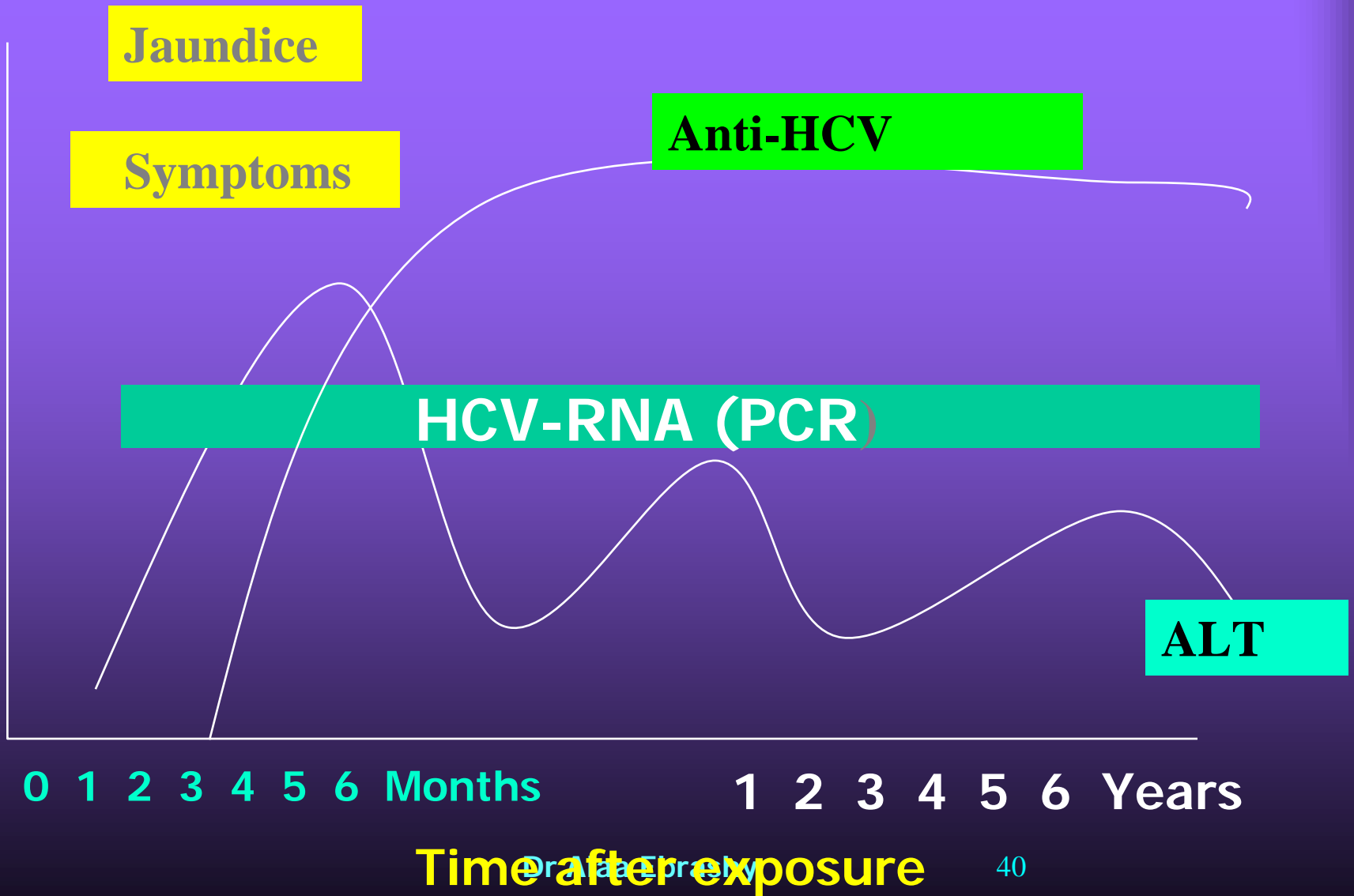
# Hepatitis C

- **Incubation period=14-140 days**
- Transmission of HCV is horizontal through parental exposure to blood and blood products and rarely vertical
- **Acute infection is almost always sub clinical and becomes chronic in over than 85% of cases**
- **HCV is rarely, if ever fulminate**
- Chronic HCV infection may be associated with extra hepatic manifestations eg arthritis, glomerulonephritis

# POSSIBLE SEQUELAE OF EXPOSURE TO HCV



# Hepatitis C



## SOURCES OF ACQUISITION OF HEPATITIS C VIRUS

### High Risk (over 20%)

- Injection drug users
- Recipients of unscreened blood products
- Transfusion of blood products that did not undergo viral inactivation

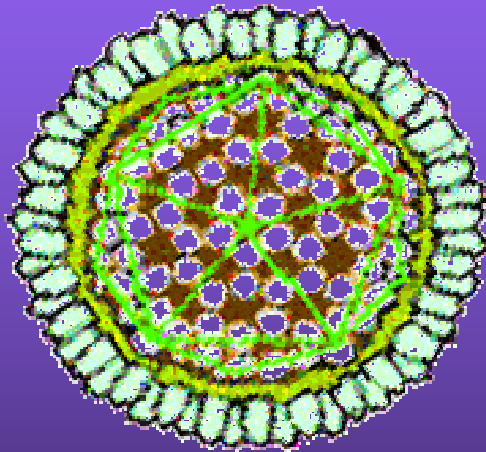
### Moderate Risk (1-20%)

- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants
- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

### Low risk (below 1%)

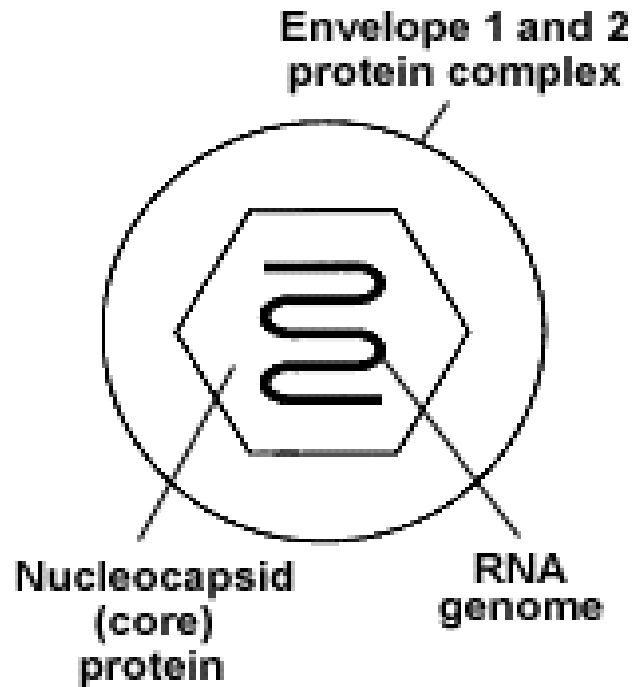
- Persons engaged in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities (such as ear and body piercing)
- Tattooing not carried out in properly regulated premises
- Household contact

# Hepatitis viruses



HBV

## HCV Viral Components

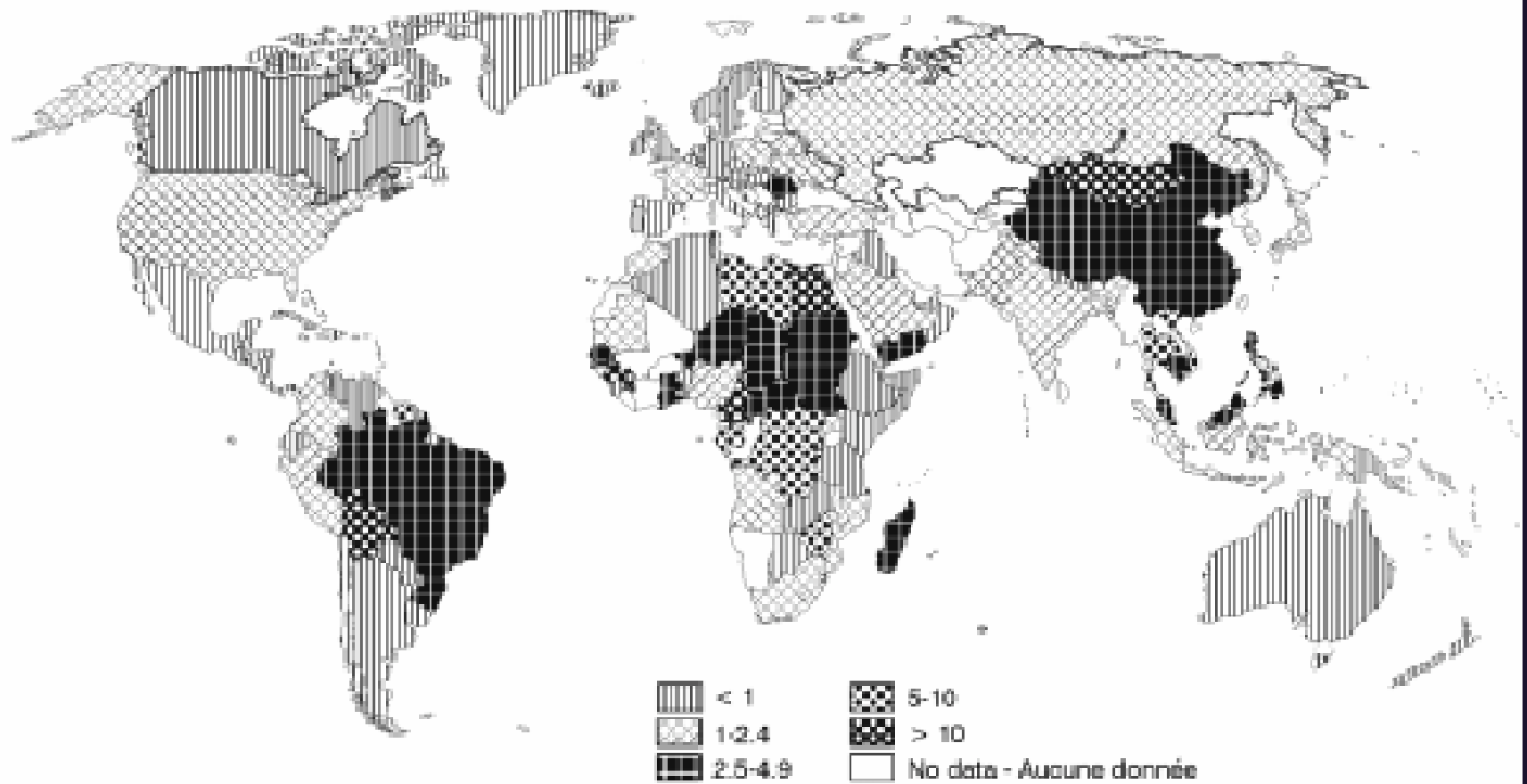


HCV



HEV

## PREVALENCE OF HCV IN DIFFERENT PARTS OF THE WORLD



# Diagnosis of acute and chronic Hepatitis C

	<b>HCV ELISA</b>	<b>HCV RIBA</b>	<b>HCV RNA</b>	<b>ALT</b>
<b>Acute</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>High</b>
<b>Chronic</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>N or abnormal</b>
<b>Recovery</b>	<b>+</b>	<b>+</b>	<b>-</b>	<b>N or abnormal</b>
<b>False +</b>	<b>+</b>	<b>-</b>	<b>-</b>	<b>Normal</b>

# Hepatitis C in Egypt

- HCV infection is a major endemic health problem in Egypt
- Egypt has the highest country wide prevalence of HCV in the world , with an estimated 8-10 million among a population of 70 million having been exposed to the virus and 5-7 million with active infection

# Hepatitis C in Egypt

- An important cause for the high exposure to HCV in Egypt was the establishment of a large reservoir of infection as a result of extensive schistosomiasis control programs that used I.V tarter emetic 20-25 years ago
- Other ways for disease spread are frequent injections ,hospital admission ,sutures , surgical procedures, IV catheterization, blood transfusion or donation, unsterilized dental instruments and Endoscopic procedures without proper sterilisation procedures

# Hepatitis C in Egypt

- In Egypt , HCV along with schistosomal parasite infection is the major risk factor for chronic liver disease .
- In most Egyptian patients ,HCV genotype 4 is highly prevalent (Halim et al 1999)

# Hepatitis C in Egypt

- In a cross sectional study with case control analysis including 5071 Egyptians ,the overall seropositivity for HCV was 31% and was significantly lower among females (13%) than among males (34% ).
- HCV PCR RNA was positive for 50% of Elisa –seropositive samples (Mostafa et al 1996).
- Only 15-20% of people infected with HCV have an acute viral hepatitis syndrome

# Hepatitis C with pregnancy

- **HCV infection** does not affect the course of pregnancy and also pregnancy does not affect the natural history of HCV unless the patient has cirrhosis with associated complications .
- **Currently available treatment for HCV** comprises alpha or lymphatoid interferon usually in combination with ribavirin (*Chemello et al 1995*)
- **However both are known to be teratogenic and are contraindicated in pregnancy .**

## Mother to child transmission For HCV

- Vertical transmission of HCV is a possibility with a calculated risk of 5% to 15%, depending on the population studied, the diagnostic tests used and the duration of follow up (*Thomas et al 1998, Gibb et al 2000*)
- Risk factors for vertical transmission include HIV co infection and high maternal HCV RNA levels of more than 1 million copies /ml (*Zannetti et al 1998, 1999*)

# Mother to child transmission For HCV

- There are no currently available vaccine for HCV, because of the great genetic variability of HCV and the likelihood that a multivalent vaccine will be required .
- In the absence of maternal treatment during pregnancy and no effective vaccination for neonates ,efforts have been focused on dealing with the obstetric variables that may increase the likelihood of viral transmission
- Avoidance of invasive procedures either during pregnancy (eg CVS –cordocentesis )or during delivery ( eg scalp electrode-scalp blood sample ) may help to prevent fetal to maternal blood exposure , however ???

# Mother to child transmission For HCV

- Mode of delivery :???: CS before rupture of membranes or Vaginal delivery :
- It is well documented now that CS before ROM is an effective measure in HIV-1 transmission to the fetus .
- But In HCV : little evidence is present to support this
- Gibb et al 2000 have given some observations to support this : he reported absence of HCV transmission in 31 women who were delivered by elective CS and this was significantly different from the 6-7% frequency of transmission observed in those with NVD or emergency CS .
- however in the view of the importance of adopting elective CS for preventing mother-child transmission of HCV it seems important that these observations should be backed up by greater number and results from other centers

# Neonates and HCV

Transmission of HCV is now recognized to occur predominantly or exclusively in the perinatal period and thus PCR assay of the infant samples collected at birth are unhelpful

PCR testing at three months provides earliest and the most conclusive evidence of both infection and lack of infection *Gibb et al 2000*

# Neonates and HCV

There are no effective methods at present to prevent transmission of the HCV at birth .So the centers for disease control and prevention (in 1998) do not recommend routine screening in pregnant women .( In endemic areas ???)

**Neonates of known anti HCV positive mothers should be tested and provided follow up**

# Breast feeding and HCV transmission

A few researchers have reported the presence of HCV RNA in breast milk.

However ,breast feeding was not found to be a risk factor for transmission , hence avoidance of breast feeding is not recommended .

Risks of transmission by breast feeding were significant only when HIV co infection was present , since breast feeding is identified as an important risk factor the transmission of HIV.

# HCV infection among Egyptian women and mother to infant transmission.

## First study (*Abdelhakim et al 2002*)

- Study design : hospital designed follow up prospective study
- 696 pregnant women : in the 3<sup>rd</sup> trimester
- Tests : HCV antibodies by ELISA . Positive cases had PCR as confirmation for infection .
- Neonates of positive mothers : PCR at birth and 6-9month of age
- Mode of delivery : according to the obstetrician with no reflection to the HCV status .

Follow up prospective study of HCV infection among Egyptian women in Egypt Adelhakim et al 2002)

## Results :

- prevalence of HCV among pregnant women was 13.8%
- Vertical transmission rate by 6-9 month was found to be 28.4%
- Mode of delivery C.S or vaginal delivery did not affect vertical transmission
- Breast feeding did not contribute to neo natal transmission
- .

# HCV infection among Egyptian women and mother to infant transmission.

## Second study (Gad et al 2000)

- Study design : hospital designed follow up prospective study -2 year period
- 2000 pregnant women : in the 3<sup>rd</sup> trimester
- Tests : HCV antibodies by EISA . Positive cases had PCR as confirmation for infection .
- Neonates of positive mothers : PCR at birth and 6-month of age
- Mode of delivery : according to the obstetrician ,no reflection to the HCV status .

## Follow up prospective study of HCV infection among Egyptian women in Egypt (Gad et al 2000)

### Results :

- prevalence of HCV among pregnant women was 7.7% (PCR FOR HCV)
- Vertical transmission rate by 6-9 month was found to be <1%
- Pregnancy in cases positive for HCV did not induce deterioration of liver disease
- HCV did not increase the risk of obstetric complication

# HCV and ART

Transmission of HCV by sexual contact is rare and inefficient

In contrast to HIV-1, only low levels of HCV RNA have been found in semen

*Debono et al 2000*

There is no evidence so far that transmission has been documented after IUI attempts or after IVF **Semperini et al 1998**

# Hepatitis D Virus

RNA Virus .Delta virus group

Three genotypes with unknown number of subtypes .

HDV may be acute or chronic dose but it dose not occur in the absence of acute or chronic HBV infection because HDV requires the HBV for coating and cell to cell spread .

Thus , HDV is the result of either acute HDV and HBV co infection or HDV infection in a chronic HBV carrier .

HDV replicates in the hepatocyte cytoplasm . liver cell injury is caused by the host immune response & possibly a direct cytopathic effect

# Hepatitis D

- **Transmission of HDV is horizontal through parental exposure to blood and blood products like HBV**
- **Acute HDV is diagnosed by Positive serum test for HDV IgM in a patient with +ve HBsAG test whereas chronic HDV have serum anti HDV IgG titer of >1 to 10000 with positive HBsAG test .**

# Hepatitis D

- **Most cases with acute HDV and HBV coinfection recover completely and develop immunity to reinfection however , HDV superinfection in a person with chronic HBV results in chronic HDV in 90% of cases**
- **The course during pregnancy is similar to that of HBV . No documented cases of vertical transmission of HDV**

## Other Hepatitis viruses

- Between 5% and 20% of cases of acute and chronic hepatitis do not appear to be caused by known hepatitis viruses ,or toxic metabolic or immune –mediated mechanisms
- **Untyped hepatitis may infect women during pregnancy and be a source of diagnostic confusion ,particularly during the 3<sup>rd</sup> trimester ,when jaundice may be a complication of PIH or a sign of Acute fatty liver of pregnancy**

# Hepatitis G, GBV-C

- **Hepatitis G (known as GB virus type C GBV-C is a parentally transmitted hepatotropic virus**
- **In a study on 47 pregnant women, HGV RNA was detected in 32% .**
- **20% of the neonates were +VE for GBV-C /HBV . despite of that , there were no clinical or biochemical signs of liver disease showed on the children .**
- **breast milk sample was negative for the virus schroter et al 2000 .**

# Conclusion

- **Viral hepatitis with pregnancy continues to be a major health issue that must be understood and well known to all Obstetricians**
- **Understanding the epidemiology of the virus , the course of the disease and its effect on pregnancy or vice versa as well as the rate of vertical transmission and the neonatal outcome helped a lot for establishment of protective means for both the mother and her child either by vaccination or prevention**

# Conclusion

- Hepatitis in endemic areas remains a major health problem and represent a continuous threat for all women during their reproductive age and their offspring who remain a reservoir for new cases through vertical transmission .
- A well organized health project on the scale of the whole nation is awaiting to be established to combat this disease with all the necessary means of prevention and vaccination



***XIX European congress  
of perinatal medicine***

