HBV & HCV in pregnancy in the Jewish & Arab populations

Prof. Rifaat Safadi

Liver Unit,

Hadassah Medical Center, Jerusalem

Viral Hepatitis Prevention Board Meeting

14-15/03/2013, Yad Hashmona Hotel, Jr

High global burden of chronic HBV & HCV infection

✓ HBV	370 million
✓ HCV	130 million
✓ HIV	33 million
✓ HIV Co Infection	6-9 million
✓ Total Viral etiologies	> 500 million

CDC

Pregnancy & HEPATITIS C

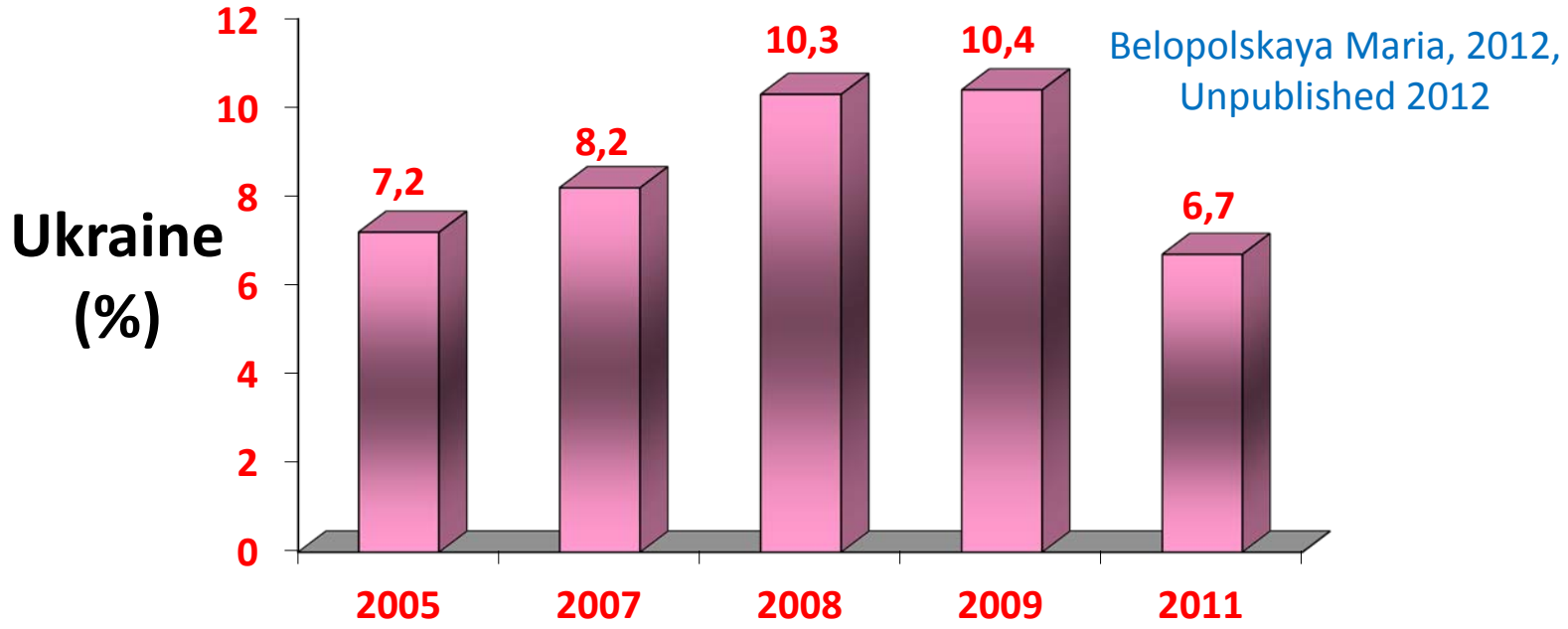
- ✓ HCV infection is a major global health issue

- ✓ Major burden from sequelae of chronic infection:
  - 3-4 million newly infected each year,
  - 130-170 million chronically infected,
  - >350,000 deaths/year

- ✓ **About 1% of pregnant women have HCV infection**

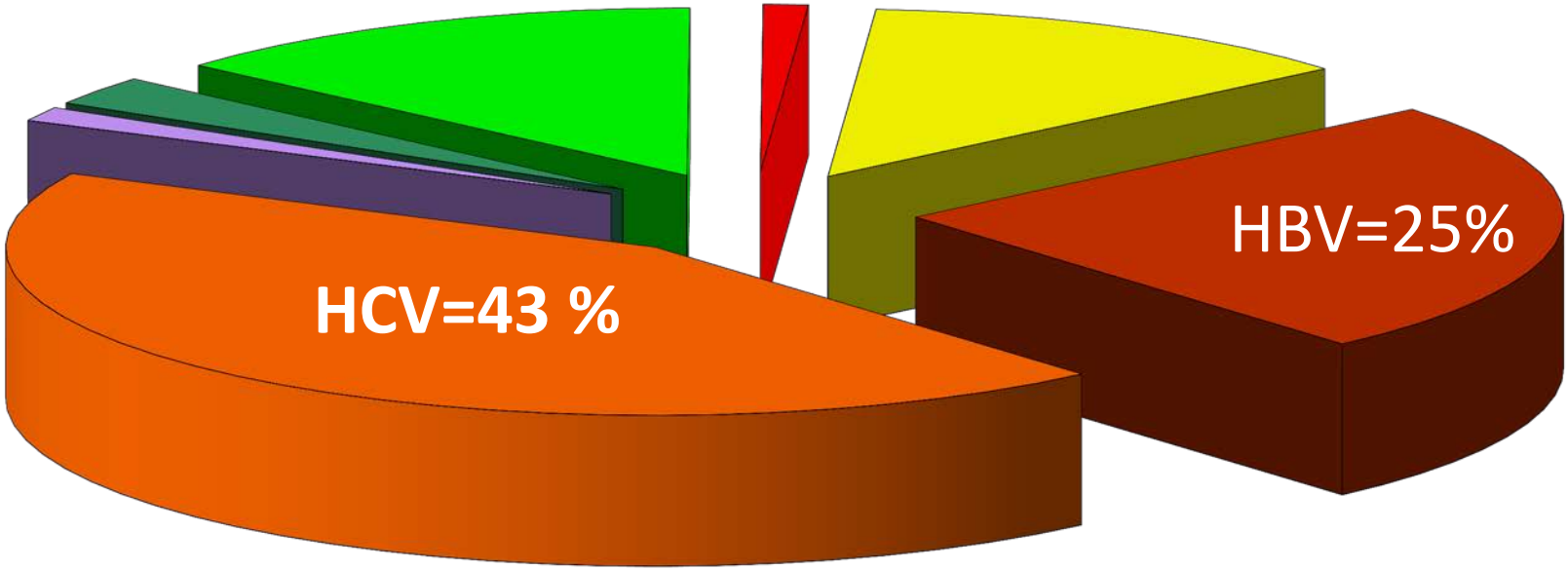
- ✓ **Corresponding to 40,000 births annually in the US**

HCV vertical transmission rates varied between 2–6% in women without HIV



Fischler B (2007) Seminars in Feral and Neonatal Medicine 12: 168–173▪
Airoldi J, (2006). Obstetrical and Gynecology Survey 61: 666–671. ▪
Hayashida A, (2007). J Obstet Gynaecol Res, 33: 417–422. ▪
McIntyre J (2006). Current Opinions Infectious Disease 19: 33–38. ▪
Capparelli E, (2005). Seminars Fetal Neonatal Medicine 10: 161–175▪

HCV Vertical transmission accounts for the vast majority of pediatric hepatic diseases



Belopolskaya Maria, 2012,
Unpublished 2012

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Risk factors of HCV vertical transmission (No obstetric risk factors)

- Mode of delivery: There is no protective effect of cesarean delivery on HCV vertical transmission compared with vaginal delivery
- Obstetric procedures: prolonged rupture of membranes may increase risk, amniocentesis unlikely to increase risk
- Prematurity: No evidence of effect

Risk factors of vertical HCV transmission (viral risk factors)

- HIV Co-infection: increases vertical transmission risk 2–3-times, although this risk can be decreased with administration HAART during pregnancy
- HCV viral load: non-viraemic women have very low risk; high viral load increases vertical transmission risk
- HCV-RNA in PBMCs (peripheral blood mononuclear cells) increases risk of vertical transmission

Belopolskaya Maria, Russia, 2012, Unpublished 2012

HCV & Pregnancy in Jerusalem 2000

A study was performed to determine the rate of HCV vertical transmission

Eur J Clin Microbiol Infect Dis (2000) 19:267–274 © Springer-Verlag 2000

Article

Transient Transmission of Hepatitis C Virus from Mothers to Newborns

M. Ketzinel-Gilad, S.L. Colodner, R. Hadary, E. Granot, D. Shouval, E. Galun

Eur J Clin Microbiol Infect Dis (2000) 19 :267–274

Methods: 22 HCV+ mothers & their 23 newborns were monitored from early after birth (No Arabs)

Mother no.	Age (years)	ALT (IU/l) (N:6–53)	Presumed route of HCV transmission	Liver disease 59%
1	37	24	blood transfusion	ND
2	32	152	not known	chronic hepatitis
3	32	63	blood transfusion	mild chronic hepatitis
4	35	93	blood transfusion	ND
5	39	21	not known	chronic hepatitis
6	41	27	health care work	ND
7	35	NA	not known	ND
8	29	73	IVDU	ND
9	27	44	not known	ND
10	23	48	not known	ND
11	27	117	blood transfusion	chronic hepatitis
12	39	57	health care work	ND
13	35	74	blood transfusion	chronic hepatitis
14	37	92	not known	chronic hepatitis
15	27	237	health care work	OLT with chronic hepatitis
16	37	133	blood transfusion	chronic hepatitis
17	35	91	not known	mild chronic hepatitis
18	40	70	health care work	chronic hepatitis
19	26	NA	not known	ND
20	36	98	spouse	ND
21	23	77	blood transfusion	active cirrhosis
22	28	NA	blood transfusion	ND

NA, not available; ND, no diagnosis available; OLT, orthotopic liver transplantation

Eur J Clin Microbiol Infect Dis (2000) 19 :267–274

Serological findings in the 22 HCV-infected mothers:

Mother no.	Anti-HAV IgG	HBsAg	Anti-HBc	Anti-HBs
1	+	−	+	+
2	−	−	−	−
3	+	−	−	+[a]
4	−	−	−	+[a]
5	+	−	+	ND
6	+	−	borderline	−
7	−	−	−	−
8	+	−	−	−
9	−	−	−	−
10	+	−	+	+
11	+	−	−	−
12	−	−	−	+[a]
13	+	−	−	−
14	−	−	+	+
15	−	−	+	+
16	+	−	+	+
17	+	−	+	+
18	+	−	−	+[a]
19	+	−	−	−
20	+	−	−	−
21	−	−	−	+
22	−	−	+	+

59% **41%**

[a] Specific anti-HBs IgG following vaccination
−, negative; +, positive; ND, not done

Eur J Clin Microbiol Infect Dis (2000) 19 :267–274

HCV findings in 23 mother-newborn pairs:
HCV antibodies & HCV-RNA

HCV-Ab's were detected in the blood of all newborns immediately after birth

HCV-RNA was detected 2 days after birth in the blood of 5 infants (22%)

However, all dropped to low or undetectable levels by 7 months of age

Eur J Clin Microbiol Infect Dis (2000) 19 :267–274

Breastfeeding in HCV+ mothers

- ✓ Is considered safe unless nipples are cracked or bleeding
- ✓ Is not recommended if the mother is HIV positive
- ✓ HCV RNA can be detected in breast milk from women with high viral load (7% when HCV RNA>10(6)IU/ml)

Belopolskaya Maria, Russia, 2012, Unpublished 2012

Pregnancy & HEPATITIS B

- HBV infection is a major global health issue
- Major burden from sequelae of chronic infection:

HBV Vertical Transmission

Universal HBV vaccination for all newborns since 1992:

Active for all neonates

Passive if maternal HBsAg+

Vertical

Israeli Guidelines for HBsAg screening

מדינת ישראל - משרד הבריאות		
שירותי בריאות הציבור		
מערכת נהלי עבודה		
שם הנוהל: נוהל לטיפול באשה הרה	מספר הנוהל/ 1/2001	
נוהל מתאריך: 21 ינואר 2001	בתוקף מיום: 1 במרץ 2001	תאריך עדכון:נוהל זה מחליף נוהל קודם מתאריך דצמבר 1993

לוח פירוט הפעילויות המומלצות לפי גיל ההריון בשבועות:

8.2.1 הבדיקות

8.2.1.1 סוג דם ו - Rh: הבדיקה תתבצע בהריון ראשון, ובהריונות הבאים רק בהעדר מידע. לנשים הרות עם Rh שלילי תעשנה שתי בדיקות ע"ש COOMBS בכל הריון: מיד עם הרשמן בתחנה והשניה בשבוע ה - 24 להריון. אשה הרה עם Rh שלילי, אשר לא פיתחה נוגדנים לגורם ה - Rh, תקבל חיסון 300 מיקרוגרם ANTI D לאחר ביצוע בדיקת סיסי שליה, אמניוצנטזיס, קורדוצנטזיס, אחרי הפלה, אחרי הריון חוץ רחמי, בשבוע ה28- להריונה, ולאחר חבלה ביטנית.

8.2.1.2 ספירת דם כללית: מומלץ לבצע הבדיקה בשבועות הראשונים להריון, בשבועות 24-28, וכן 6 שבועות לאחר הלידה.

8.2.1.3 סוכר דם בצום: מומלץ לבצע הבדיקה בשבועות הראשונים להריון. רמת סוכר > 105 מג%

8.2.1.7 HBsAg: יבוצע בקבוצת סיכון ועל פי התוויה רפואית ברורה

HBsAg should be screened in population at risk and according to an obvious indication

8.2.1.8 HIV: יבוצע בקבוצת סכון לפי הנחיות חוזר ראש שרות מס' 98-4.

8.2.1.9 טי"י זקס: הבדיקה מומלצת באוכלוסיות בסיכון גבוה, רק אם לא נערכה כבר בעבר, הבדיקה תיערך במקומות ובמועדים המתפרסמים על פי תוכנית שנתית מעודכנת של משרד הבריאות.

8.2.1.10 תלסמיה: על פי תוצאות ספירת דם כללית ישלחו בני זוג לבדיקות נוספות לאישור נשאות המחלה באוכלוסיות מיועדות שנקבעו.

8.2.1.11 בדיקות גנטיות: בגלל שינויים ועדכונים מתמידים בבדיקות הגנטיות השונות, יש לעיין בתדריכים המעודכנים.

8.2.1.12 בדיקות טרום לידתיות: א.יש להפנות כל אישה הרה אשר הגיעה לגיל 35 שנה ומעלה בתחילת ההריון ליעוץ גנטי.

נערך ע"י	אושר ע"י	חתימה:	דף מספר 4 מתוך 6
פר' דרורית הוכנר פר' יונה אמיתי בשיתוף עם הסיעוד בבריזה"צ והאיגוד הישראלי למיילדות וגניקולוגיה	דר' אלכס לבנטל		

Outline

- Overview of Hepatitis B in Pregnancy
  - Epidemiology
  - Natural History and Outcomes in pregnancy
  - HIV/HBV in Pregnancy
  - Perinatal transmission
- Israeli Data

The prevalence of HBsAg+ in Pregnancy

Low:

- ✓ US (<2%)
- ✓ African-American women- 1%
- ✓ Caucasian women - 0.6%
- ✓ Latina women- 0.14%

High:

- ✓ **China: ~10%**
- ✓ **India: 1-9%**
- ✓ **Thailand 3-8%**
- ✓ **South Africa: 2-5%**
- ✓ **Cote D'Ivoire: 8%**
- ✓ **Uganda 5%**
- ✓ **Asian women- 6%**

Sinha Hepatology Res 2010

HBeAg+ Prevalence in Pregnant HBV Women (Africa)

HBeAg (%)	Country
<2%	Ethiopia, Ghana, Nigeria
3.3%	Zimbabwe
4.6%	South Africa
9.5%	Senegal
16.1%	Zambia
24%	Southern Tanzania

Sinha Hepatology Research 2010

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Impact of HBV on Pregnancy Outcomes

Yes: Association with:

- ✓ Increased gestational diabetes
- ✓ lower Apgar scores[1,2]

No: No association with adverse pregnancy outcomes[3-5]

1. Lao J Hepatol 2007
2. Tse J Hepatol 2005
3. Pastorek AJOG 1988
4. Wong Am J Perinatol 1999
5. To Aust N Z J Obstet Gynaecol 2003

Impact of HBV on Pregnancy: Maternal Liver Disease

- ✓ **Liver disease:**
  - No liver disease worsening in majority of women[1]
  - Case reports[2-4] of:
    - Hepatic exacerbations
    - Fulminant hepatic failures

1. Terrault NA, et al. Semin Liver Dis. 2007;(suppl 1):18-24
2. Mahtab MA, et al. Hepatobiliary Pancreat Dis Int. 2008;7:161-164.
3. Yang YB, et al. World J Gastroenterol. 2004;10:2305-2306
4. Rawal BK, et al. Lancet. 1991;337:364.

Impact of Pregnancy on HBV

- **HBV DNA levels**
  - Overall increase in median HBV DNA levels during pregnancy (n=55)[1]
    - 4/16 (20%) HBeAg negative women had > 1 log increase in HBV DNA during pregnancy
    - Even with lamivudine therapy
      - 7.8 log10 copies/mL → 8.2 log10 copies/mL during pregnancy (P = 0.06), despite lamivudine therapy in 13 patients[2]

1. Soderstrom SJID 2003
2. ter Borg JViralHep 2007

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What is known about HIV & HBV in pregnancy?

- ✓ **Prevalence**
  - South Africa: 2.4%
  - Uganda: 4.9%
  - Zambia: 7.1%
  - Cote D'Ivoire: 9%

Barth Int J Infec Diseases 2010

HIV progresses HBV disease

- ✓ Higher HBV replication (HBV DNA & HBeAg+)[1]
- ✓ Lower rate[4] of
  - spontaneous loss of HBeAg
  - spontaneous loss of HBsAg
  - seroconversion to anti-HBe and anti-HBs
- ✓ Lower ALT levels[4]

1. Bodsworth NJ et al. J Infect Dis 1989
2. Thio et al Lancet 2002 2. Bodsworth NJ, et al. J Infect Dis 1991.
3. Hadler SC et al. J Infect Dis 1991.
4. Gilson RJ et al. AIDS 1997.

Therefor, in HIV HBV co infection

- ✓ Higher rate of chronicity[2,3]
  - ✓ 20 to 80% as compared to 3-5% in HIV -
  - ✓ increased risk with low CD4 at time of HBV acquisition
- ✓ Higher incidence of lamivudine resistance[4]
- ✓ Faster progression to cirrhosis[4]
- ✓ Higher mortality (compared to HIV or HBV mono infection)[2]

1. Bodsworth NJ et al. J Infect Dis 1989
2. Thio et al Lancet 2002 2. Bodsworth NJ, et al. J Infect Dis 1991.
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When HBV Transmissions Happen?

- ✓ **In utero (<10%)**[1]: Associated with risk factors:
  - Acute HBV in third trimester
  - High Maternal Replication: HBeAg & high HBV DNA
  - History of threatened preterm labor
  - HBV in the placenta

- ✓ **At the time of delivery**[1]
  - HBeAg-positive mothers: 85%
  - HBeAg-negative mothers: 31%

- ✓ **After birth**
  - Breastfeeding is not associated with transmission[2]

1. Gambarin-Gelwan Clinics Liv Disease 2007
2. Beasley Lancet 1975

HBV Transmission is Prevented by Postnatal Vaccination

	No Vaccine	Passive Immunization	Passive+Active Immunization are most effective
Infants with HBV	95%	28%	5%

	Without immunoprophylaxis	HBIG & HBV vaccine series
HBeAg positive	70-90%	5-10%
HBeAg negative	10-40%	<5%

Ranger-Rogez S, et al. Expert Rev Ant Infect Ther. 2004;2:133-145.

Failures of Prophylaxis: Why?

- ✓ High maternal viral load
- ✓ Surface antigen mutations (e.g. G145R)
- ✓ Vaccine-related
  - Poor quality assurance/storage
  - Failure to complete schedule of vaccine

High maternal viral load

- ✓ **Role of maternal HBV DNA on transmission[1,2]:**

  > HBV DNA 1.1 x 10^7 IU/mL = 32% transmission

  < HBV DNA 1.1 x 10^7 IU/mL = 0% transmission

- ✓ **HIV/ HBV co infection had higher viremia[3]**

1. del Canho R, et al. Vaccine. 1997;15:1624-1630
2. Wiseman E, et al. Med J Aust 2009
3. Bodsworth NJ et al. J Infect Dis 1989

Prevention of HBV Transmission by maternal anti viral therapy

Pregnancy Category of FDA-Approved Treatments for Chronic HBV

Drug	Pregnancy Category
IFN alfa-2b	C
PegIFN alfa-2a	C
Adefovir	C
Entecavir	C
Lamivudine	C
Telbivudine	B
Tenofovir	B

Drugs [package insert].

Lamivudine Treatment During Pregnancy

LAM given 1 month before delivery decreased HBV transmission:

- ✓ **from 28.0%** in untreated historical controls
- ✓ **to 12.5%** (OR: 2.9; 95% CI: 0.29-28.0)

  - ✓ All received standard prophylaxis
  - ✓ No adverse events noted with LAM

van Zonneveld M, et al. J Viral Hepat. 2003;10:294-297.

Telbivudine Treatment During Pregnancy

- **At birth:**
  - undetectable HBV DNA but HBsAg+ were 13(10%) Vs. 19(20%)
  - seropositive HBV DNA & HBsAg+ were 0 Vs. 9

- **At 7 month:**
  - seropositive HBV DNA & HBsAg+ were 0 Vs. 7
  - detectable anti-HBs

    132/132 (100%) Vs. 81/88 (92%) (t=10.845, P=0.001)

- **The transmission rate were 0% (0/132) in telbivudine and 8% (7/88) in control group (t=10.845, P=0.001)**

G.R.Han. et al, Journal of Hepatology, 2011

Tenofovir for prevention of HBV vertical transmission by highly viremic women

A retrospective study (2008-10) in 11 Asian HBV mono infected HBeAg+, pregnant women who received TDF in the third trimester.

A significant HBV-DNA reduction at delivery

All 11 infants received Active/Passive vaccination had no obstetric complication or birth defects.

<u>All were HBsAg negative 28-36 wks after birth</u>

Dig Dis Sci. 2012 Sep;57(9):2423-9

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Reported hepatitis B carriage rate in gravid women in Israel

- ✓ Is in the range of 0.6–4%
- ✓ With rates varying among ethnic groups

Zamir C, Dagan R, Zamir D, et al. Evaluation of screening for hepatitis B surface antigen during pregnancy in a population with a high prevalence of hepatitis B surface antigen-positive/hepatitis B e antigen-negative carriers. Pediatr Infect Dis J 1999; 18(Suppl. 3): 262–6.

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Methods:

A population-based study in Negev women who delivered during the years 1988–2007, compared:

✓HBsAg and/or anti-HCV seropositive women
✓ with all other pregnant women in the same period

Multivariable logistic regression models were constructed to control for confounders

Liver International (2010)

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Results:

749 hepatitis seropositive pregnant women were identified out of 186 619 deliveries **(0.4%!!!)**.

Maternal characteristics, as well as perinatal outcomes, were comparable between the HBV and HCV carriers.

Liver International (2010)

Comparison of characteristics between hepatitis carriers and non-carriers groups

Characteristics	Hepatitis carrier ($n = 749$) (%)	Comparison group ($n = 185\,870$) (%)	*P*-value
Maternal age (years)			
≤ 18	0.7	1.1	< 0.001
19–35	80.0	86.2	
36+	19.3	12.7	
Birth weight (g)			
< 2500	10.4	7.8	0.029
2500–4000	84.5	87.3	
> 4000	5.1	4.8	
Low birth weight (< 2500 g)	11.2	19.3	0.06
Drug abuse	2.9	.0	< 0.001
Ethnicity			
Jewish	81.7	54.1	< 0.001
Bedouin	18.3	45.9	
Preterm delivery (< 37 weeks)	9.9	16.9	0.08

Data are expressed as meansstandard deviation (SD), or numbers and percentages

The relative low rates of hepatitis carriers found in this study may represent an underdiagnosis in general and the Bedouins in particular

Liver International (2010)

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Results:

HBV/HCV carriers had significantly higher rates of:

- Preterm deliveries (Po37 weeks gestation; 11.5 vs. 7.9%, Po0.001)
- Premature rupture of membranes (8.9 vs. 6.9%, P = 0.026)
- Placental abruption (1.5 vs. 0.7%, P = 0.018)
- Labor induction (33.9 vs. 28.1%, Po0.001)
- Caesarean deliveries (19.0 vs. 13.2%, Po0.001)
- Perinatal mortality (2.3 vs. 1.3%, P = 0.016)
- Congenital malformations (7.2 vs. 5.1%, P = 0.01)
- Cases with low birth weight (o2500 kg; 10.4 vs. 7.8%, P = 0.009)

Liver International (2010)

Vertical HBV transmission in Jerusalem within the vaccine era

R Michaiel[1,2], R Calderon Margalit[2], E Shteyer[3], Y Ashur[4] & **R Safadi[1]**

1. Liver Unit, Institute of Gastroenterology and Liver Diseases, Division of Medicine. Hadassah- Hebrew University Medical Center, Jerusalem.
2. Braun School of Public Health and Community Medicine, Hebrew University-Hadassah, Jerusalem 91120, Israel.
3. Pediatric Gastroenterology Unit, Division of Pediatric, Hadassah-Hebrew University Medical Center, Jerusalem
4. Clalit Health Services, Jerusalem

Accounts ~77% of Arabic JR population

Safadi R, Harefua, 2013

A cross-sectional descriptive study was conducted in the year 2005-2006 at Clalit Health Services, Jerusalem

Children at age ≥1 year born after 1992 for HBsAg positive mothers were evaluated.

<u>During the year 2005:</u>

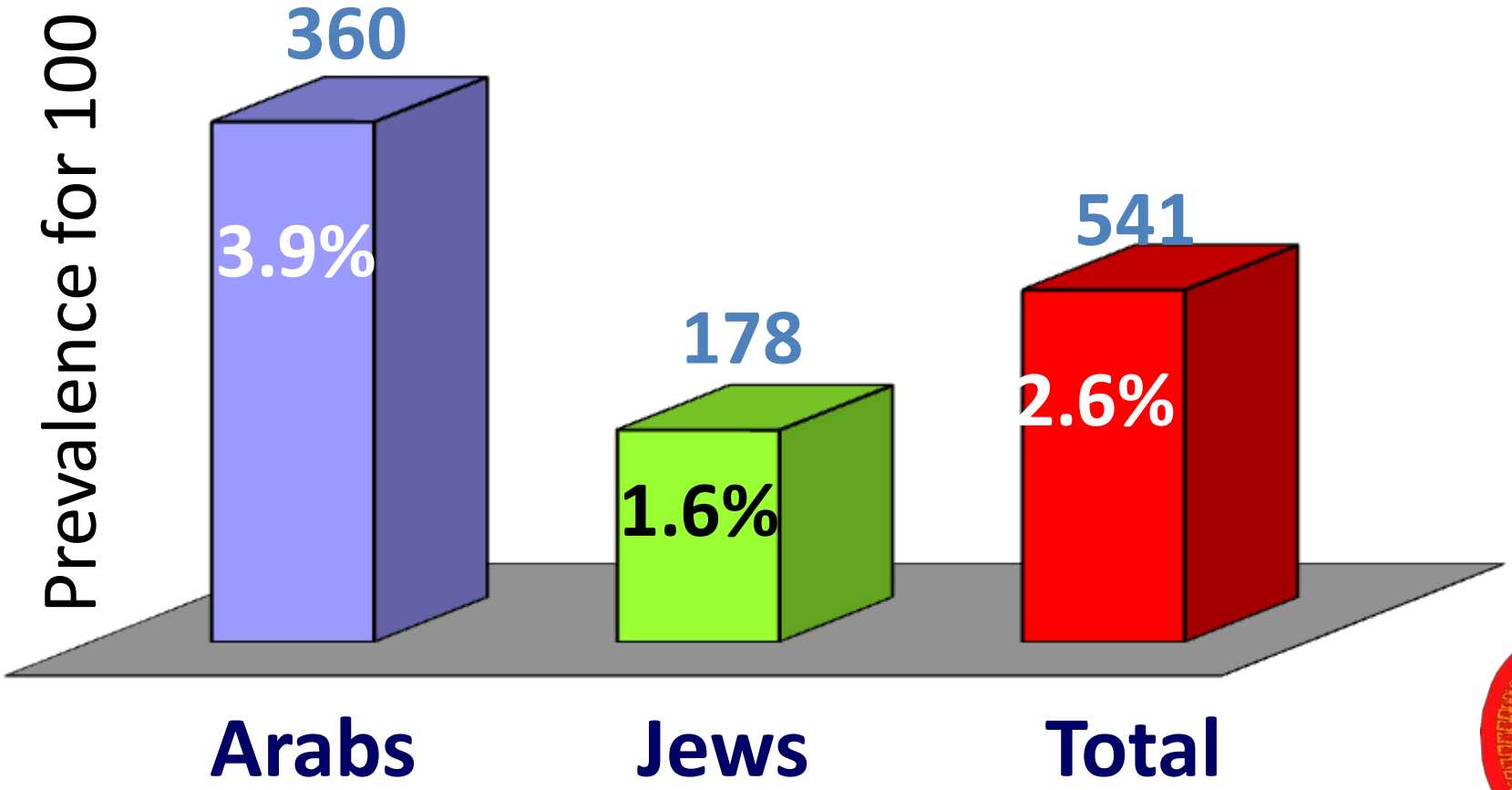
20,415 members were screened for HBV:

- 55% (11,186/20415) were Jewish.
- 45% (9,229/20,415) were Arab.

Safadi R, Harefua, 2013

HBsAg+ prevalence 2.64% among the general Jerusalem population (95%CI, 2.43-2.87)

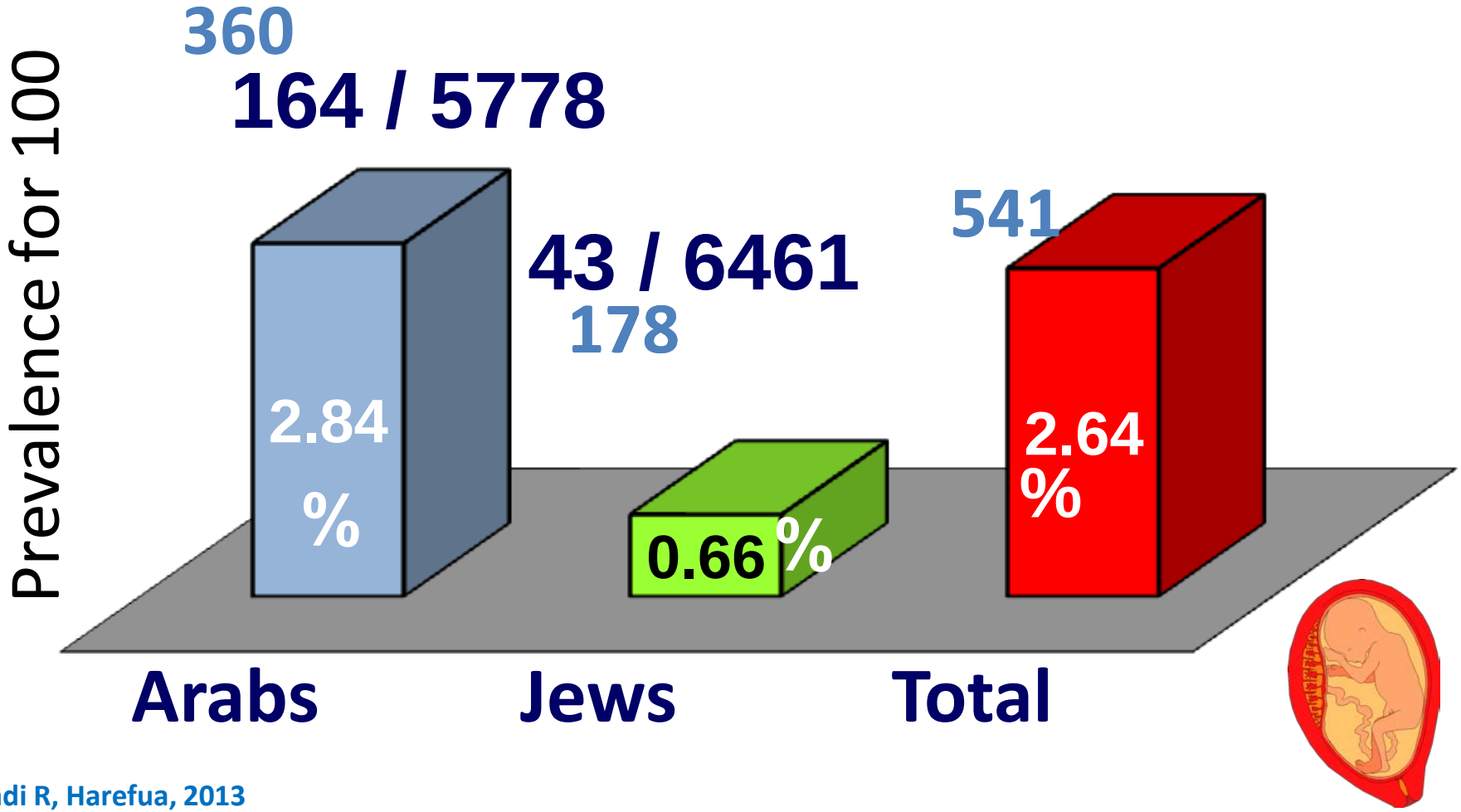
- ✓ 3.9% among the Arabs (95%CI, 3.34-4.34);
- ✓ 1.59% (95%CI, 1.37-1.84) among the Jewish population



Safadi R, Harefua, 2013

HBsAg+ state in fertile women age 18-44 y

- ✓ 1.7% (total);
- ✓ 2.84% (95%CI, 2.43-3.3) in Arabs
- ✓ 0.66% (95%CI, 0.48-0.9) among Jewish women



Safadi R, Harefua, 2013

Of 164 Arab HBsAg+ fertile women, we identified 157 mothers for 409 children at age ≥1 year born after 1992

Data for 188 children to 70 mothers was collected:

- HBsAg
- HBc-Total Ab'S
- HBs-Ab's

The prevalence of vertical infection among the children cohort

- Positive anti-HBc was 8.4% (95%CI, 4.71-13.1)
- positive HBsAg) was 4.4% (95%CI, 1.8-7.6)

Safadi R, Harefua, 2013

37.1% of these children had negative anti-HBs titters

- ✓ 41.4% with anti-HBs 11-100 mIU/ml
- ✓ 21.5% with titters above anti-HBs 100mIU/ml.

- ✓ 48% (23/48) children received passive-active vaccination
- ✓ 35% (17/48) children received only active vaccination

- ✓ 12.5% (6/48) were born to mothers prior to HBV infection diagnosis and received only the active vaccine.

- ✓ 4.5% (2/48) received no vaccination at all.

Safadi R, Harefua, 2013

Failures of Prophylaxis: Why?

- ✓ High maternal viral load
- ✓ Surface antigen mutations (e.g. G145R)
- ✓ Vaccine-related
  - Poor quality assurance/storage
  - Failure to complete schedule of vaccine

History of Hepatitis B Vaccines

Generations

1st

Plasma-derived

-HBsAg, Pre-S

2nd

Yeast-derived,

HBsAg

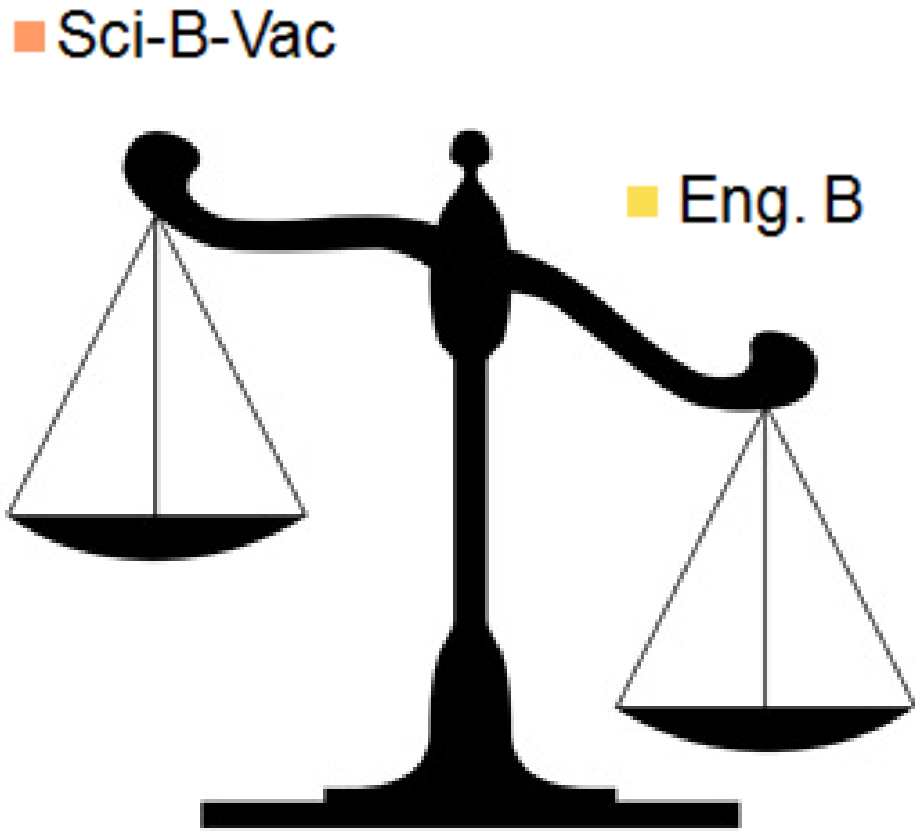
3rd

Mammalian cell d.

-HBsAg, Pre-S2

HBsAg, Pre-S2, Pre-S1

recombinant



Summary

Proposed Recommendations for HBV-Infected Women Who Desire Pregnancy

- ✓ Women with mild liver disease, low viremia
  - Pregnancy before treatment
- ✓ Women with moderate liver disease, no cirrhosis
  - Treatment before pregnancy; if response, stop treatment before pregnancy
- ✓ Women with advanced liver disease
  - Treatment before and during pregnancy; continue treatment after delivery

Wedemeyer H, et al. Dtsch Med Wochenschr. 2007;132:1775-1782.
EASL Clinical Practice Guidelines. J Hepatol.

Strategies to Further Reduce Vertical Transmission: Role of Antiviral Therapy?

Women with mild liver disease, very high viremia

- Treatment in last trimester with “B” category drug with post-partum discontinuation

1. van Zonneveld M, et al. J Viral Hepat. 2003;10:294-297.

Thank You

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