MY REFERENCE BOOK IN OBSTETRICS

NIELS JØRGEN SECHER
PROFESSOR
Department of Obstetrics and Gynecology
Copenhagen University Hospital in Hvidovre
2650 Hvidovre
E-mail: njsecher@dadlnet.dk

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FOREWORD

This manual is a combination of Guidelines and Protocols of patient management in Obstetrics.
I hope it will be a concise reference, readily accessible in a clinical setting, decreasing the need to access a detailed textbook, which may not always be available.
I compiled this manual in order to refresh my memory regarding the complex medical cases we see, and in an attempt not to omit any important steps in the management or treatment of these cases.
These guidelines are not the official protocols of Copenhagen University Hospital at Hvidovre, but they express my personal opinions and are as 'evidence based' as possible.
I wish to thank my colleagues at King Faisal Specialist Hospital, Kingdom of Saudi Arabia, who helped me with the first edition, when I worked there as the Chairman, and my colleagues in Denmark (the Sandbjerg Guidelines and Guidelines at Hvidovre Hospital) as well as my secretaries Ms. Zenaida C. Viktoria, Mette Krøll and Karen Eckhoff, who painstakingly dedicated their time and effort in completing this reference.
Thanks to my young colleagues Birger Breum, B. Baldur-Felskov, Suher Hassan, Bo Rud and R. Svetlana for their input.
I also want to thank Lars Krag Moeller, MD for his comments and making it possible to see the book on the Internet at: http://www.gyncph.dk/secher/index.htm

Niels J. Secher, MD
Professor
Department of Obstetrics and Gynecology
Copenhagen University Hospital in Hvidovre
Denmark
E-mail: njsecher@dadlnet.dk

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Antiphospholipid syndrome(APS) (Acgurred Acquired thrombophilia)

Definition: Criteria for the classification of the APS:
At least one of the following clinical criteria and one of the following paraclinical/laboratorial criteria should be met:

Clinical Criteria:

1. Vascular thrombosis and/or

2. Pregnancy morbidity (Poor Obstetric History)
   a) Unexplained death of a morphologically normal fetus at or beyond 10 weeks.
   b) One or more premature deliveries before 34 week of gestation because of severe preeclampsia/eclampsia or severe IUGR.
   c) Three or more unexplained consecutive abortions before 10 weeks of gestation (controversial, if no fetal heart has been seen, as some believe that very early abortion is not caused by APS)

Paraclinical/laboratory Criteria:
The presence of Antiphospholipid antibody (aPL) on two or more occations at least 12 weeks apart

Antiphospholipid (aPL) antibodies:

- Lupus anticoagulant (LA) directed against phospholipidbinding plasm proteins prolonged activated partial thromboplastin time.
- Beta 2- glycoprotein-1 antibodies, β2-GP >99th percentile
- Anticardiolipin (aCL) antibody

Medium titer: 20 - 50 anticardiolipin IgG and 20 -80 anticardiolipin IgM.

Secondary Antiphospholipid Syndrome: When antibodies is found in association with systemic lupus (SLE) (see also page 63), other rheumatic disease, autoimmune disorders, infections and medicine.

Prevalence:
2 - 5% of all pregnant women have cardiolipin antibodies or lupus anticoagulant but very few have antiphospholipid syndrome.
30% of women with severe early onset preeclampsia may have antiphospholipid antibodies.

Background:
Anticardiolipin antibodies react with proteins bound to phospholipids in the cell membrane such as cardiolipin. Different isotypes and subclasses are associated with aCL including IgA, IgM, and IgG subclasses 1 to 4. Elevated levels of IgG anticardiolipin antibodies (particularly IgG2) incur a greater risk.

Risks:
Maternal thromboembolism is highly variable and exacerbated by co-existent hereditary coagulopathies. In one study thrombosis during pregnancy was 5% among women with known antiphospholipid syndrome.

Preeclampsia:
Occurs in one third of women with severe preeclampsia before 34 weeks. The relative risk is about 10 for developing preeclampsia in case of antiphospholipid syndrome.
Recurrent abortion and fetal loss, especially among women with a history of thrombosis and high titers.

Evaluation:
Who should be evaluated for antiphospholipid syndrome? Bad Obstetric History:

- more than 2 ≥ 3 abortions
- Unexpected fetal death after 16 weeks
- Severe IUGR
- Severe preeclampsia/eclampsia before 34 weeks

Indication for investigation:

- Pregnancy complication as above
- Major abruption of the placenta
- Big placental infarction
- False positive syphilis serologies

Medical Conditions:

- Non-traumatic thromboembolism, stroke, Systemic lupus erythematosus, Hemolytic anemia, transient ischemic attacks, amaurosis fugax, and libido reticularis.
- Unexplained prolongations of the activated partial thromboplastine time (aPTT) or PT
- Unexplained thrombocytopenia.

Treatment:
Women with APS and history of thrombosis should already be permanently anticoagulated (most are given Warfarin, INR 2-3)
Low-dose aspirin, preconception and during pregnancy.

If permanently anticoagulated:
Heparin, LMWH in therapeutical dosis and low dose asperin.
If not on permanent anticoagulation:
Prophylactic dose of LMWH and low dose asperin. Same treatment if obstrical complications and lupus anticoagaulant (LA) or high anticardiolipin antibodies

Low molecular heparin (LMWH) or Heparin when pregnancy is confirmed (before 6 weeks to avord Wafarin induced emhyopathy) and stop 6 weeks postpartum in case of previous thrombosis or 5 days after birth if no previous thrombosis.
Heparin stopped once labour has begun and restarted 6 hours post delivery.
See also prophylactic dose and therapeutic dose of Heparin under thrombophilia (page 99) and thromboembolism and prophylaxis in pregnancy (page 101).
Consider discontinuing heparin at 20 weeks gestation if uterine artery waveforms are normal and the indication for Heparin is not very strong.

Osteoporosis prevention in Heparin treated women: Vitamin D 800 mg 1500 mg Ca carbonate and weight bearing active i.e: walking are recommended.

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BLEEDING ANTEPARTUM

Definition: Bleeding after 20 weeks of gestation.

Assessment on Arrival:

1. Maternal Condition:
   (a) Degree of Shock
   (b) Blood Pressure/Pulse
   (c) Active Bleeding
   (d) Abdominal palpation
   (e) Vaginal inspection, if appropriate
   (f) Hemoglobin
   (g) Platelet and Coagulation factor
   (h) Urine Output/proteinuria
2. Fetal Condition:
   (i) Viability/Presence of Fetal Heart
   (a) Probable Gestational Age
   (b) Quality Fetal Heart (CTG)
3. Ultrasound assessment:
   (a) Singleton presentation
   (b) Placental Site
   (c) Estimated Fetal Weight
4. Probable Etiology:
   Association with hypertension, trauma, etc.

Resuscitation and Volume Replacements:

In case of major obstetric haemorrhage

1. IV access 2 x 14 or 16 cannulas see page 12.
2. O2 BY MASK, 8 l/min.
3. Elevate legs
4. Blood for:
   - Cross match (6 units of blood)
   - Full blood count
   - Clotting screen (fibrinogen, APTT, PT, D-dimer, platelets)
   - Base line urea and electrolytes

Foley catheter (monitor hourly urine output)
Monitor (most optimal continuous monitoring): pulse, blood pressure, O2 saturation, ECG, pulse oximeter, central line

Volume Replacement
See page 12: Suggestion for blood replacement and preparation for the use of Novoseven.

Abruptio Placenta
Clinical diagnosis and not a diagnosis based on ultrasound.

Symptoms:
Pain, uterine hypertonous, local or generalized.
Uterine irritability, bleeding (15% concealed).

Type I Slight vaginal bleeding and some uterine irritability is usually present. Maternal and fetal condition not affected.

Type II Mild to moderate vaginal bleeding with living fetus, uterus is irritable and may be tetanic, signs of fetal distress, pulse rate may be elevated and coagulopathy (DIC) as well as pre-shock can develop.

Type III a) Fetal death. Moderate to severe bleeding. (concealed bleeding: uterus Couve-laire), and b) uterus tetanic and fetal type and mother in shock with coagulopathy (DIC).

II Trimester Management/Inspection concerning affection on the cervix: erosion, polyp, cancer (contact bleeding), cervix dilatation (cervix insufficiency, labor). If recurrent bleeding on the cervix, colposcopy, Pap smear in a non-bleeding stage.

III Trimester - As above, but ruled out placenta previa/abruptio in case of preterm delivery consider gestational age.

Management:

Type I Admission under observation. IV access, CTG, expected management if mother and fetus are in good condition and there is no sign of tachycardia or coagulopathy. Eventually artificial rupture of the membranes if cervix is ripe and gestational > 35 weeks and/or if early labor to prevent further abruption.

Type II Caesarean Section, eventually artificial rupture of the membranes in the waiting time. Vaginal delivery if delivery can be anticipated within 1-2 hours and fetal heart can carefully and constantly be monitored if contraction are poor, augment labour with oxytocin.

Type III Correction of hypovolemia and coagulopathy, cesarean section or induction by artificial rupture of membranes and cautious with IV Oxytocin.

Postpartum Oxytocin infusion and control of coagulation factors in case of Type II and Type III. Careful monitoring of renal factor.

Be prepared for post partum haemorrhage**.**

Recurrance Risk is 15% .

Placenta Previa.

Do not perform vaginal examination unless preparation have been made for immediate Caesarean section

Risk increased with age, parity and uterine surgery.

Diagnosis:

Unstable lie and mono-symptomatic bleeding.
Ultrasound: Transvaginal is safe and is more accurate than transabdominal ultrasound in locating the placenta.

II Trimester:
5-6% in late second trimester
Potential placenta previa; cover internal orifice especially if > 1/3 of placenta is covered

III Trimester:
0.1-0.5% in third trimester.
Total: > 1 cm cover internal orifice.
Marginal: < 1 cm from internal orifice.
Low-lying placenta 1-3 cm from internal orifice.

Treatment:
< 1 cm from internal orifice always c/s
1-2 cm – a high percentage end by emergency c/s because of bleeding especially if thick placental margin
> 2 cm can expect normal delivery.

Ruptured ulterus:

- Restore blood volume
- When stable immediately perform lapecstomy and deliver the baby and placenta.
- If the uterus can be repaired with less operative risk than hysterectomy would entail and if the edges of tear are not necrotic, repair the uterus.
- Otherwise perform subtotal hysterectomy or if tears extends ? cervix and vagina total hysterectomy may be requested.

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BLEEDING POST PARTUM

Definition: More than one liter.

Causes: Atony obs. distended bladder
Retention of placenta, placenta accreta
Obstetric Trauma (Hematoma, Rupture and Laceration)
Coagulopathy
Distended Bladder

Diagnosis of placenta accreta before birth: In previous cesarean section: Ultrasound show the hypoechoic boundary is lost and the placenta appears contagious with the bladder wall. Color flow Doppler and MR may be used as adjunctive diagnostic tools.

Treatment: Massage of the uterus until hard and give oxyticin 10 IE/IM or directly in the uteris and slowly IV
Placenta Out by controlled cord traction if unsuccesfull remove placenta manualy. Give appropiate IV/IM antibiotics.
Inspection
Coagulation status: Thrombocytes, APTT, PP, fibrinogen, D-dimer, ATIH if bleeding is in progress (aggressive)

Two large bore IV line, Foley catheter, Oxygen by mask
3-4 liters crystalloids, replace 1 liter blood if shock with systolic blood pressure less than 90 mm Hg, pulse faster than 110 beats 1 Litre fluid in 15 minuts (as rapid as possible).

If no match blood available, use O-Rhesus negative until available
Fresh frozen plasma if more than 6 units of red cells given
Give thrombocytes if platelets is less than 50,000 or bleeding more than 5 l.
Cryoprecipitate as indicated
Cyklocapron 1 g i.v.

Novoseven (factor VII a) for uncontrolled bleeding (see the table):
Before use, correct for acidosis and acidenia. In case of continuously bleeding, use Novoseven, but thrombocytes (> 5 mia/l) and Fibrinogen (> 3 μg/l) has to be available. Therefore the acute package can be used. This consist of 5 SAG-M + 5 FFP (or Fibrinogen 2 g (30 ml/kg) or co-precipitate as indicated) and 2 package of thrombocytes concentrate 5 ml/kg and give 50 μg/kg Novoseven over 2-3 minutes. If thrombocytes is not available, use 100 μg/kg.
Repeat: Coagulation-status after 10 minutes if still bleeding.
CAVE: Plasma expanders can decrease the effect of Novoseven.
Risk: Trombocytes is contra-indicated if DIC caused by sepsis because of hypercoagulopati.

Inverted uterus:
Reposition should be performed immediately as a contruction ring around the uteris if more rigid and more engored with blood.
IV fluid and pethedin 1 mg/kg IV or IM (max 100 mg).
Do not give oxytocin until inversion is corrected.
Manual reposition if possible in anaesthesia.

Hydrostatic repositioning:

Exclused uterine rupture, unfuse warm saline by rubber tube held 1-2 metre about patiens (an assistant blocks the vaginal office) give tocylitica nitroglycerin subhycial/absilan IV.

Surgical reposition (laperotomy):

Alice forceps in the dumple of the inverted uterus and upword traction (Huntington procedure) or cut the ring posterior using longitudinal incision (Haultains procedure).

Suggestion for blood replacement and preparation for the use of Novoseven (Sandbjerg 2005)

Blood loss % of volume (100 % = 5-6 l for 60 kg woman)	Replacement	Volume	Total	
0-20 % → 1 l	Nacl isotonic 1000 ml x 3	3000		
20 – 50 % → 2,5 l	RBC suspension x 2	600	2	
	Synthetic plasma substitutes	1000		
50 – 90 % → 4,5 l	RBC suspension x 4	1200	+ 4	
	FFP x 2	600		
90 – 100 % → 5 l	RBC suspension x 2	600	+ 2	Prepare for Novoseven *
	FFP x 3	600		
> 100 % → 5 l	RBC suspension x 4	1200	+ 4	
	Thrombocytes x 2 pools			
	Fibrinogen 2 g or FFP 10-20 ml/kg x 5			
	*			Novoseven 50 μg/kg i.v. over 2-3 minutes
* Eventual repetition of above mentioned before Novoseven				
	Thrombocytes x 2 pools			
	RBC suspension x 4	1200	4	
	Fibrinogen 2 g *or* FFP 10-20 ml/kg			
	Cyklocapron 1 g			

Novoseven can be repeated after 20 minutes

Oxytocin Oxytocin 10 IU slowly intravenous (cave hypotension) or intramyometrial
Oxytocin infusion 20 units in 500 cc 30-60 drops/minute.
Methergin 0.2 mg (cave hypertension and coronary insufficiency), repeat after 15 minutes. Maximum dose 1 mg.
15-Methyl $PGF_{2\alpha}$ Hemabate (0.25 mg IM/intramyometrial) repeated after 15 minutes not more than 2 mg (cave asthma,hypertension, severe heart disease, liver disease and glaucoma)
Misoprostol 2-5 tablets rectally
Tachyphylaxis can develop and different receptors involved so use more than one type if no effect

Bimanual Compression or Aorta Compression

Intrauterine Tamponade for 24-48 hours, the vagina should be packed as well

Uterine artery embolization

Laparotomy

B-Lynch suture.
Multiple square suturing from an arbitrary point in the heavily bleeding area is selected and the entire uterine wall from the serosa of the anterior wall to the serosa of the posterior wall is included, 2-3 cm between insertions.
Stepwise ligation of uterine artery including the parametrium and 2-3 cm of the lateral wall of the uterus below and over the transversical incision and finally uteroovarian vessels
Ligation of hypogastric artery (secure pulse in femoral artery)
Subtal or total hysterectomy, the transition zone between cervix and uterus can be felt like a bulk.
Intraabdominal-pelvic packing with 10-12 laparotomy pads for 24-48 hours

In case of placenta accreta/percreta

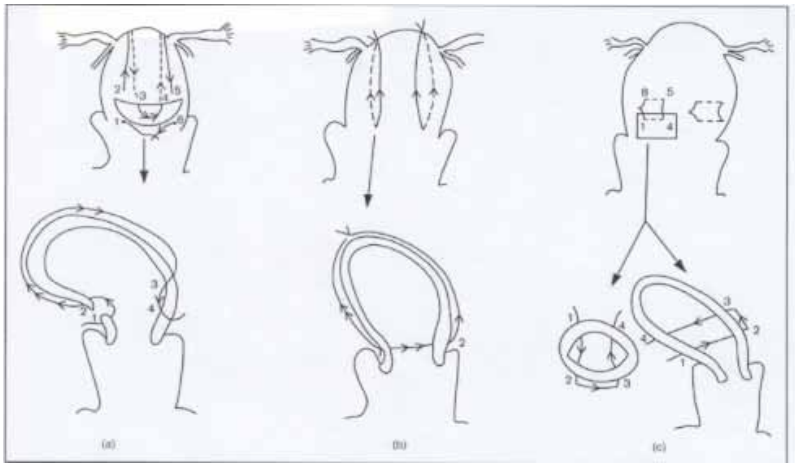
Leave the placenta or cotyledons
Suturing the placenta side
Oxytocin, hemabate and/or vasopressin in the placenta bed
Balloon catheter with 400-500 cc
I have usedTachosil supplemented with uterin packing with good results.

Paravaginal Haematoma
Infralevatoria Haematoma
Incision preferable in vagina and evacuation followed by suture only if the bleeding is easily detected following by packing of the cavity and the vagina (for compression). Removed after 8-24 hours.

Supralevatorial Haematoma
Incision and packing only close the vagina partially. Vaginal and sometimes uterine packing (stretch the uterine artery).

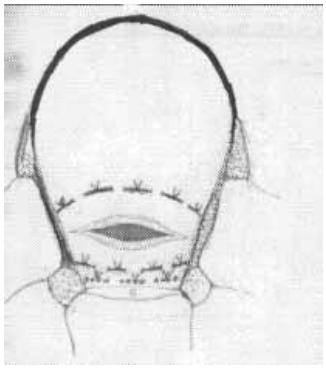
Supbperitoneal Haematoma
Observation: If not progressing wait hours for not to get bleeding when the haematoma is incised Expl. Lap. or ultrasound guided). It can be necessary to do ligation of the anterior part of the internal iliacal artery (secure pulse in the femoral artery) can also be done by arterial embolisation.

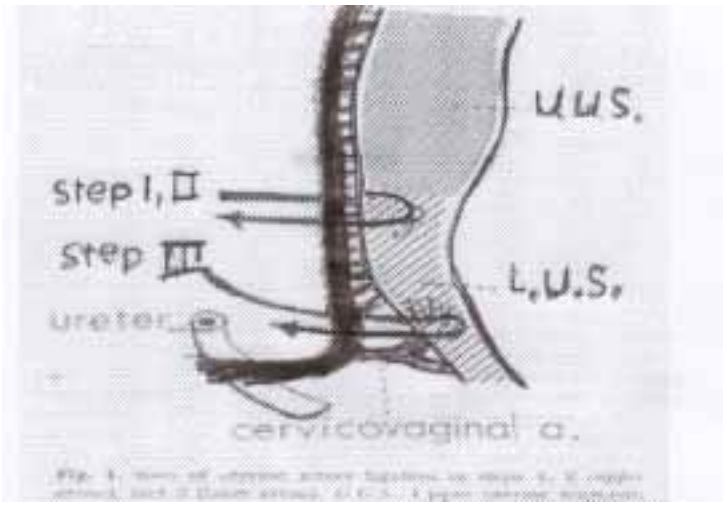
Uterine Haemostatic Suturing Techniques (a) B-Lynch; (b) modified B-Lynch; (c) modified square



A FLAPPY NON-BLEEDING UTERUS SHOULD NOT BE REMOVED AFTER UTERINE SUTURES IF BLEEDING HAS STOPPED

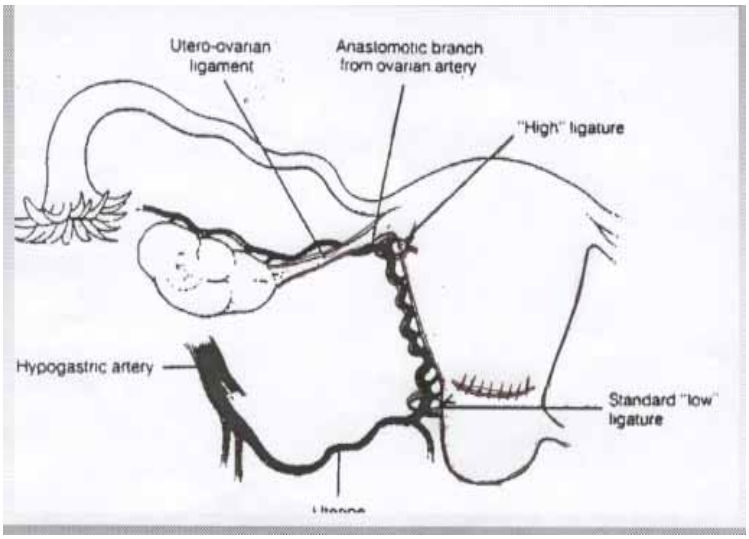
Interrupted circular suture for the anterior lower segment bladder





Stepwise Uterine Devascularization

Stepwise Uterine Devascularization



Uterine Artery Ligation

3 Steps: Uni or bilateral ligature of uterine artery

Uni or bilaterial ligature of descending branch of uterine artery

Uni or bilateral ligature of the anastomosis from ovarian artery

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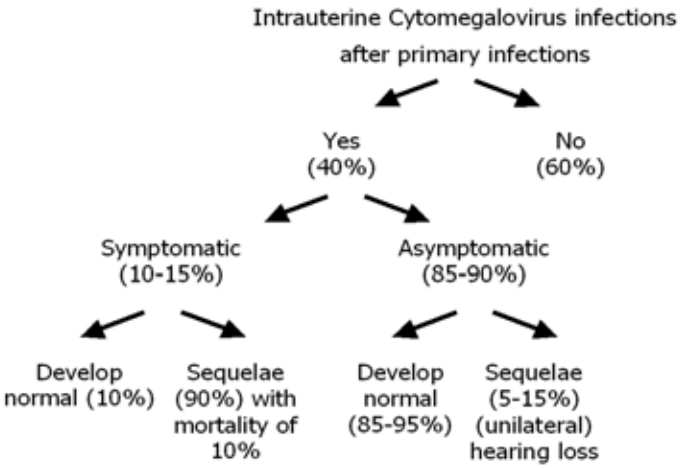
Cytomegalovirus

Incidense
60%-80% have had CMV infections in developed countries and nearly 100% in developing countries.
Intrauterine infection occurs in 0.5%-2% in Europe, and 10-15 % of congenital infected newborns will have symptoms. Approximately 10-20% die and at least two thirds will have neurological involvement. Hearing loos can be seen in infants asymptomatic at birth.

IF THE MOTHER GETS THE CMV PRIMARY INFECTION



Maternal symptoms:
Incubation period 4-8 weeks. Most common asymptomatic or monucleosis-like symptoms can develop specially in immuno-incompetent mothers.
Intrauterine infections after primary infections occur in 33% in the first trimester and 44% in the third trimester.

7% of woman with primary infection will have badly damaged fetus with congenital CMV.
CMV can be present in breast milk with between 25% and 70% of seropositive women shedding CMV in some stage. CMV is rarely found in colostrum. If CMV is isolated in the milk, the risk of acquisition of infection is high (50 percent) but sequelae for child small.
In case of congenital cytomegalovirus infection half of the mothers have a primary infection. More than half of mothers have antibodies against CMV.
Contagious only if intimate contact (kiss, coitus, labour, breastfeeding, etc.) CMV shedding in the saliva and urine in day care centers from 10-80 %.
Infected infant excretes virus in saliva and urine for several years.

Transmission:

More likely to these who shed CMV from the cervix or the vagina at the time of delivery and estimated 50% of infants born to these mother can acquire the infection. Repeat infection of an infant in the next pregnancy is extremely seldom. Infections postpartum are harmless. The extremely premature infants have been identified as a risk for severe infections.

Ultrasound Markers:
Cerebral ventriculomegaly. Micro cephalic hyper-echogenic bowel hepatosplenomegaly, ascitis, intracranial calcification, IUGR but normal ultrasound does not exclude neonatal abnormality.
One half of symptomatic infants will present with the syndrome of cytomegalic inclusion diseases, consisting of:

- Jaundice - 67 percent
- Hepatosplenomegaly - 60 percent
- Petechial rash - 76 percent
- IUGR - 50 percent
- Thrombocytopenic purpura - 18 percent.
- Multiorgan involvement (e.g. microcephaly, motor disability,chorioretinitis, periventricular leukomalaci and calcifications, hydranencephaly, optic atrophy, lethargy distress and seizures)

Jaundice and hepatosplenomegaly may subside but neurologic sequelae (e.g. microcephaly, cerebral palsy, mental retardation, hearing loss, chorioretinit is not progressive as in toxoplasmosis) may persist. In case of fulminant presentation, mortality can be up to 10 percent and occurs within a few days or weeks.
The other half of symptomatic patients present with a more attenuated form of congenital infection, consisting usually of isolated splenomegaly, jaundice and/or petechiae.
More than 80 percent of infants symptomatic at birth will develop late complications that may include hearing loss, vision impairment and varying degrees of mental retardation and delay in psychomotor development.
Infections acquired in late pregnancy may have less prominent signs, although severe developmental problems associated with CNS like: calcification, microcephaly, and hearing loss have been reported.

Diagnosis:
Unfortunately, conventional serological test for CMV is not as straight forward as test for other viral infections. IgM can be detected up to 9 months after primary infection and reappear during reactivation. Contact biologist in case of suspected CMV infection. High avidity IgG indicate no evidence of active infection (IgM and IgG positive) only 30% IGM positive has a primary infection. If IGM is negative and IgG positive no infection the last 4-6 weeks.

- ☐ If only IgM positiv repeat test to confirm the infection.
- ☐ Amniocentesis PCR 6-5 weeks after infection
- ☐ Demonstration by PCR tells that the infant is infected but not if affected.

However, a high viral load (assessed by quantitative PCR) suggests symptomatic fetal disease.

Neonatal infections:
Virus demonstrated (Virus culture, CMV-ANA(PCR) or CMV-IgM) (urine, blood, tissue) the first 2 weeks after delivery indicates congenital infection. It takes normally one to three days of incubation to get the answer for culture. CMV-IgM can be demonstrated in 70%

of infants with congenital CMV and in all who later develops sequelae. CMV DNA, using PCR probably identify the infants that need to be followed up for neurological assessment and hearing loss.

PROPHYLAX
No risk to staff if normal hygiene is achieved.
Do not kiss other children on the mouth and do not taste the spoon during feeding. Do not eat the children's leftover.

Treatment:
No treatment recommended, but promising results has been found on preventing a high percentage of later hearing loss with treatment with ganciclovir of newborns.
The use of anti-CMV hyperimmune globulin for treatment and preventing of congenital infection are promising. Oral valganciclovir is under investigation.

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(5) www.uptodate.com 2007

Diabetes in pregnancy

Classification:
Type I Insulin dependent diabetes mellitus (IDDM)
Type II Non-Insulin dependent diabetes mellitus (NIDDM)
Type III Gestational diabetes mellitus (GDM) or Carbohydrate. Intolerance (± Insulin)
First recognized in pregnancy (True and Pre-existing diabetes)
Type IV Secondary diabetes.

Gestational Diabetes
Definition: Glucose intolerance with onset first recognized in pregnancy
Incidence: Variable (1-30%) depending on the level of glucose intolerance used and the ethnicity of the population (United States 2-5%, Denmark 2-3 %). Compared to North European, 11-fold increase in woman from India, 8-fold in Southeast Asia, 6-fold in Arabs, 3-fold in Afro-Caribbean.

Diagnosis:
Risk factors (detects >95% of women with GDA).

- ☐ Glucosuria: 2+ Boehringer, 1+ Multistix, >5,5 mmol/L
- ☐ Previous gestational diabetes (33-50% recurrent risk)
- ☐ Obesity (BMI > 26,9 kg/m2)
- ☐ Family disposition (first degree relative)
- ☐ Previous macrosomic baby (>4499 gr) or large for date baby in current pregnancy
- ☐ In Denmark one of the above risk factors in 36% of the population. Sensitivity 83%. Specificily 65%
- ☐ Some also suggest unexplained stillbirth malformation, age > 35 years preterm delivery, and polyhydramnios

Glucose Tolerance Test:
The later in pregnancy the higher the detection rate.
Screening is optimally performed at 24-28 weeks of gestation.
Earlier (in 14-20 weeks) if high degree of suspicion, previous gestational diabetes or 2 of the following 3 criterias:

- ☐ Obesity
- ☐ Previous macrosomia
- ☐ Family disposition

Blood-glucose = plasma-glucose x 0.86
A fasting plasma glucose level > 7.0 mmol/L (126 mg/dl) or a random plasma > 11.1 mmol/L (200 mg/dl) meets the threshold for the diagnosis of gestational diabetes if confirmed on a subsequent day and precludes the need for any glucose challenge test.
When to perform OGTT based on a plasma glucose and glucosuria:
75 mg OGTT if glucosuria (≥ 2+ with Boehinger or ≥ 1+ with Bayer), random venous plasma glucose should be recorded.

WHO advise oral 75 mg glucose tolerance test should be carried out if blood glucose is >5.5mmol/L 2 hours or more after food or > 7 mmol within two hours of food.

CRITERIA: There is no consensus regarding the criteria for the 75 g OGTT in pregnancy.

CRITERIA FOR DIAGNOSIS OF GDM WITH THE 75 G OGTT

Organization	Fasting	1 h PG	2 h PG	Diagnostic Criteria for GDM
WHO	>6,9 mmol/L (126 mg/dL)	Not Measured	>7.7 mmol/L (140 mg/dL)	One abnormal value
Fourth International Workshop/ ADA 1982	>5.2 mmol/L (95 mg/dL)	>9,9mmol/L (180 mg/dL)	>8.5mmol/L (155 mg/dL)	Two or more abnormal values
National Diabetes Data Group (NDDS) 2000	>5.7 mmol/L (95 mg/dL)	>10.5 mmol/L (190 mg/dL)	>9.1 mmol/L (160 mg/dL)	GDM: Two or more abnormal values IGT: One abnormal value

PG: Post glucose ADA: American Diabetes Association NDDS: Diabetes care 2000, suppl 1 S:4

ADA: Random glucose level > 11,1 (200 mg) or fasting >7,0 (126 mg) diagnostic of diabetes Danish guidelines >8,9 mmol in capillary blood or venous plasma.
In Denmark we define a 2-hour level < 9 mmol/L (162 mg/dL) as normal and will repeat the procedure if glucosuria occurs.

Importance of Prognosis: Someone will have preexisting diabetes and therefore first detected during pregnancy.
Decrease incidence of macrosomia (30% of GDA) and shoulder dystocia if diet, insulin and induction are applied.
40-60% developed NIDDM within 15 years and 10-30% would have established eye or renal disease at that time. Modification of lifestyle and diet may prevent or delay NIDDM.
Clinical fasting glucose postnatally to look for onset of NIDDM.

MANAGEMENT:
Exercise – in some women the need for insulin may be obligated.
Diet - decrease calorie level
Fiber rich diet
Carbohydrate 55% of total calories
Protein 75-100 gm daily
Fat < 30%, Optimal < 15%
Calories
35 calories per kilo: folic acid a least 1 mg/daily

Obese patients 25 calories per kilo but not < 1800 cal/day
Opthalmoscopy before pregnancy and during each trimester is advised. HbA1C levels (< 8%, 5% risk of malformation, > 10%, 25% risk). 24 hours creatinine clearance and protein.
CTG non stress at 35 weeks earlier, if indicated.
Ultrasound in first trimester, 22 weeks (malformation) inclusive cardiac scan if NIDDM/IDDM

Blood glucose monitoring

Medical Management:
Blood glucose monitoring, aim to have blood glucose between 4 and 7 mmol/L.
Fasting < 6 mmol and 90 minuts after meals < 8 mmol, mean values before and after breakfast and lunch should be less than 7 mmol.
The American College of Obstetricians and Gynecologist recommend the administration of insulin to reduce the risk of macrosomia if one hour postpranded glucose > 130-140 mg/dl /7,2-7,8 mmol/l). HbA1C < 6-7% before 20 weeks and 5-6% after 20 weeks.

Dietitian/Diabetic Nurse, if medical nutritional treatment gives fasting > 5.3 mmol/L (95 mg) or 2-hour > 6.1 mmol/L (120 mg) insulin should be considered.

Insulin

Subcutaneous	Onset (hr)	Peak (max.effect) (hr)	Duration (hr)
Regular	1	2-3	4-5
NPH	2	8	24

Regular Insulin Half-Lives

- ☐ Intravenous regular insulin: 5 minute half-life
- ☐ Intramuscular regular insulin: 2 hour half-life
- ☐ Subcutaneous regular insulin: 4 hour half-life

1) If the desired level of blood sugar is not reached by diet, insulin should be added
2) Almost always use NPH and regular insulin in AM and PM
3) Usually need twice as much in AM than PM
4) Alternative regimen the evening dose is to administer regular insulin before dinner and NPH at bed time to avoid nocturnal hypoglycemia.
   Some give regular insulin before meals and NPA at bedtime.
5) Some patients may require additional regular insulin before lunch to reach the goal of euglycemia state
6) 2 weekly mild attacks of hypoglycemia are acceptable

Insulin with target levels

Danish Recommendation
4.0-6.0 mmol fasting
(3-6 before meals)
3-8 after meals
3,5-6 middle of the night
6-8 before bedtime

Outcome such as birthweight, correlates better with postprandial than preprandial glucose levels and correlates better to the level of HbA1C.
Sliding Scale Checking BSS every 2 hours, and give regular s.c. insulin, as below:

Blood sugar mmol/L	**Action**

6,6-8,0	No Insulin Regular
8,1-10	02 IU Insulin Regular
10,1-12	04 IU Insulin Regular
12,1-14	06 IU Insulin Regular
14,1-16	08 IU Insulin Regular
> 15	10 IU Insulin Regular
	Call Physician especially if also ++ or +++ ketonuria and give insulin

Steroids and Insulin: Insulin requirement is increased. The above algoritm can be used.

Diabetic ketoacidosis (DKA)
Diabetic ketoacidosis is an acute metabolic and obstetric emergency that can jeopardize both mother and fetus. Normally treated in ICU.
Fetal mortality as high as 50%.

The clinical features of DKA are due to:

1) Marked dehydration
2) Acidosis
3) Electrolyte disturbance

Presenting signs and symptoms of DKA:

4) Vomiting
5) Polydipsia
6) Polyuria
7) Weakness
8) Abdominal pain
9) Weight loss
10) Hyperventilation
11) Dry mucus membranes
12) Tachycardia
13) Hypotension
14) Disorientation
15) Coma
16) Underlying infection

Labotory Findings:
Pregnant patient can develop DKA with glucose level less than 20 mg/dl.
Tab I

Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

	DKA			HHS
	Mild	Moderate	Severe	

Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)•	Variable	Variable	Variable	>320
Anion gap♙	>10	>12	>12	<12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

* Nitroprusside reaction method.
• Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.
♙Calculation: (Na+) - (Cl- + HCO3-) (mEq/L). See text for details.

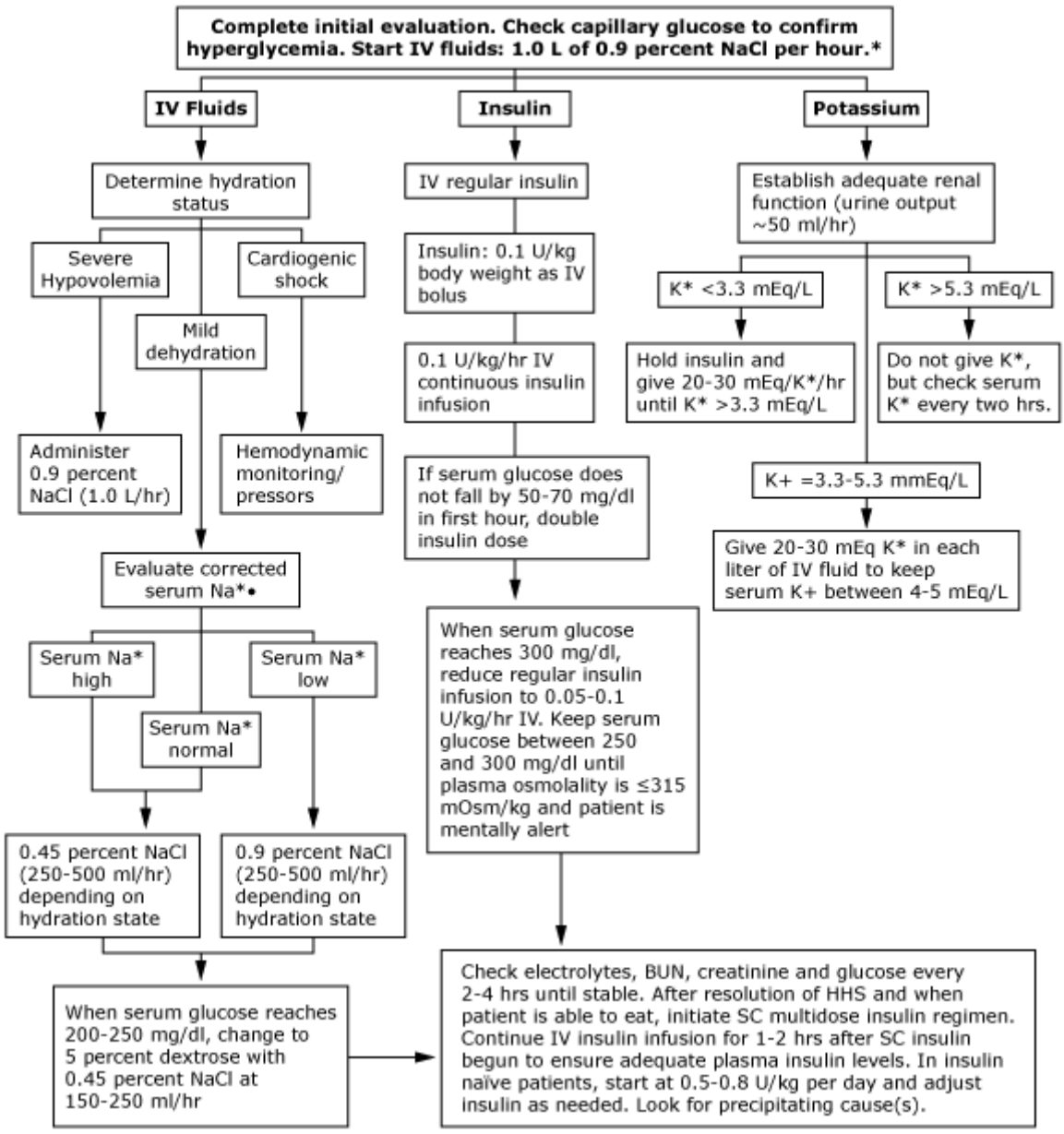
Additional atory Findings
Glucosuria
Leukocytosis
Ketonuria
Elevated CPK
Metabolic acidosis
Elevated amylase
Hyperosmolarity
Elevated transaminase
Hypokalemia
Elevated BUN
Hypomagnesemia
Elevated Creatinine
Hypophosphatemia

Monitoring
Serum glucose, serum ketones, arterial blood gas, creatinine, HCO2, serum electrolytes, anion gap, BUN, pulse oximetry, Urinary output Repeat blood and urine test frequently Place patient in left lateral position Monitor fetal heart rate Check for evidence of infection
If in coma/stupor O_2 nasal cather.

Specific Treatments

Tabel II

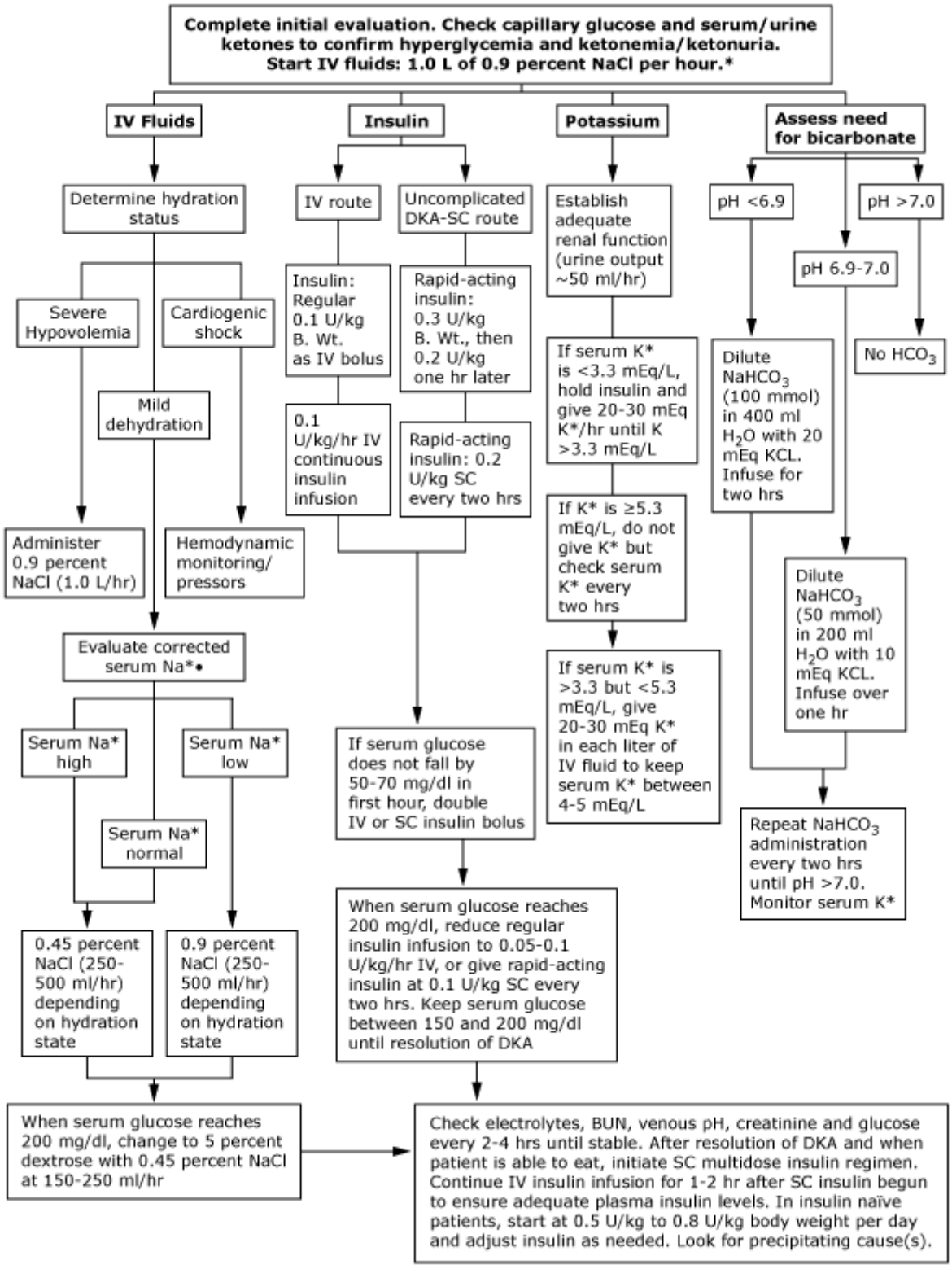
Protocol for the management of adult patients with HHS



HHS diagnostic criteria: serum glucose >600 mg/dl, arterial pH >7.3, serum bicarbonate >15 mEq/l, and minimal ketonuria and ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.
IV: intravenous; SC: subcutaneous.
* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin one liter of 0.9 percent NaCl over one hour and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile and creatinine levels STAT. Obtain electrocardiogram, chest X-ray, and specimens for bacterial cultures, as needed.
•Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value).

Tab III

Protocol for the management of adult patients with DKA



DKA diagnostic criteria: serum glucose >250 mg/dl, arterial pH <7.3, serum bicarbonate <18 mEq/l, and moderate ketonuria or ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.
IV: intravenous; SC: subcutaneous.
* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin one liter of 0.9 percent NaCl over one hour and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest X-ray, and specimens for bacterial cultures, as needed.
•Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value).
American Diabetes Association From Diabetes Care Vol 29, Issue 12, 2006.

Management of diabetes

1. Fuld diet

2. Calculate the total number of insulin units administered over 24 hours following stabilization

Total units/day

Before breakfast	Distribution
1/3 of total units / day	2/3 NPH 1/3 Regular
.	.
Before dinner	½ NPH
1/3 og total units/day	½ Regular

(NPH may be given at bedtime instead of at dinner of hypoglycemia occurs at 3 AM)

Hypoglycemia

The increased risk of hypoglycemia during pregnancy occurs in:

- Early pregnancy; first trimester
- During sleep
- Patient with previous history of hypoglycemia

Symptoms

- Tachycardia
- Tremor
- Hunger
- Pallor
- Dizziness
- Irritability
- Nausea
- Headache
- Paraesthesia
- Concentration & memory loss
- Confusion

- Somnolence Stupor, convulsions and coma

Treatment
One glass of apple juice and extra bread
Less than 6 mmol before sleep give extra bread
Unconscious
Give 100 to 200 cc isotonic glucose or (20-50 cc 20%) and if difficult give Gluca Gen 1 mg im
Elective delivery for poorly control diabetes before 38 weeks.

Timing of Delivery
Induction of labour before 40 week should be limited to those maternal or fetal complications that necessitate delivery before 40 weeks.
Estimated fetal weight of 4500 or more Cesarean delivery should be considered.

Indication for IOL before 40 weeks
- ☐ Poor metabolic control
- ☐ Diabetic patient with vascular disease
- ☐ Poor compliance
- ☐ Premature stillbirth
- ☐ Progressing retinopathy
- ☐ Fetal reson as macrosome

If preterm occurs in pregnant diabetic, tocolytic therapy with parenteral B-sympathomimetic agents is best avoided and Indomethacin and/or Oxytocin antagonist should be used (steroids and insulin).

Insulin and delivery
Continuous infusion of both insulin and glucose has been proven valuable to control maternal glucose levels during and delivery.

In patients with well-controlled diabetes who are scheduled for induction of or elective Cesarean delivery the usual dose of insulin is given at bedtime; and morning insulin is withheld in patients with less than 20 U. Insulin can be discharged.
In Denmark we prefer to give the patient normal diet and insulin until she is in a state of induction and then keep fasting with iv. Glucose 60 ml/h and insulin on sliding scale every 4 hour as shown below. If Caesarean section 1/2 to 1/3 of morning insulin as insulin retard and then iv. glucose and sliding scale as above.

One unit of insulin decrease the glucose level by ~ 1 mmol/l.

The dose of insulin and the fluids:

Blood glucose (Mm/l)	Insulin Dosage (u/hr)	Fluids 125/hr
5,5	0	Dextrose/Lactated Ringer
5,5-7-7	1	Dextrose/Lactated Ringer
7,8-10	1,5	Normal saline
10-12	2	Normal saline
>12	2,5	Normal saline

Continuous electronic fetal heart rate monitoring
Avoid Foley catheter, if possible.

Postpartum Aspects * IV Maintenance
Continue intrapartum intravenous solution until next scheduled meal and other reason to maintain IV line (stopping IV without providing other carbohydrates source may result in hypoglycemia).

* **Insulin**

1. Up to 80% of diabetics newly diagnosed in pregnancy will not need insulin postpartum. Many insulin dependent diabetics will have markedly reduced requirements after delivery.
2. One-half of pre-pregnant long action insulin dose only when one can be certain patient is eating diet.
3. When using the sliding scale - only give 5 - 10 units for 4+ urine glucose; no insulin for 3+ urine glucose. Unless acetone, then 5 - 10 units.
4. Adjust until desired blood glucose control. a.FBS< 7 mmo/L b.2 hr PPBS in 8-11 mmol/L range
5. Regular diet postpartum unless elevated plasma glucose. For obese women, low caloric weight reduction diets are initiated at 2 weeks postpartum if not lactating.
6. On at least 50% give 1/3 insulin as before delivery and after 1-3 month the insulin requirement is as before pregnancy. Keep the BS between 5-10 mmol fasting as well as before or after meals.

If	**Give antropid**
BS > 12	2 IE
BS > 14	4 IE
BS > 16	6 IE
BS > 18	8 IE
BS > 20	10 IE

   Breastfeeding is not contraindicated. Lactating women-add 200 kcal/day to antepartum calorie level.
7. If not breastfeeding, decreases antepartum diet by 300 kcal/day. Further modification of calories for attaining and/or maintaining desirable body weight is made at 2 weeks.
8. Schedule FBS to do a formal GTT at postpartum check-up (8 weeks)

VALUES FOR POSTPARTUM 75 G GLUCOSE TOLERANCE TEST

.	Diabetes Mellitus	Impaired Gluc. Tolerance (IGT)	Impaired Fasting Glycaemia (IFG)
Fasting plasma glucose (FPG)	>6,9 mmol/L (126 mg/dL)	>6,9 mmol/L (126 mg/dL)	>6.0 mmol/L (110 mg/dL)
	or	and	<7.0mmol/L (126 mg/dL)
2-hour 75 g value	>11.1 mmol/L (200mg/dL)	>7.8mmol/L (140 mg/dL) <11.1 mmol/L (200 mg/dL)	>7.7mmol/L (140 mg/dL)

Adapted from WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications
☐ Remember Preconceptional Counseling
Annual fasting blood glucose postnatally to look for onset of NIDDM as 40 % develop NIDDM within 7 years and up to 60 % within 15 years and 10-30% would have

established eye and/or renal disease at that time. Modification of lifestyle and diet may prevent or delay NIDDM.

References:

(1) Feig Palda VA. Type 2 Diabetes in Pregnancy: A growing concern. Lancet 2002, 359:1690

(2) Jensen, DM et al Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. Am J Obstet Gynecol 2003 Jul;189(1):239-44

(3) Jensen, DM et al. Diabetes Care. 2004 Dec;27(12):2819-23.

(4) Kapoor, N. et al. Diabetes in pregnancy: A review of current enduve current evidence, Curr Opin Obstet Gynecol, 2007 Dec;19(6): 5586-90.

(5) Lauenborg et al. Incidence of diabetes after gestational diabetes: a long-term follow-up in a Danish population. Diabetes Care. 2004 May;27(5):1194-9.

(6) Management of Diabetes. Scottish Intercollegiate, Guidelines Network, November 2001.

(7) Nelson-Piercy, C. Handbook of Obstetric Medicine. Published in the United Kingdom in 2002 by Martin Dunitz Ltd.

(8) Oats JJN. & delivery. In: Diabetes and pregnancy. An international approach to diagnosis and management. Eds. Dornhorst A, Hadden DR, John Wiley & Sons, New York 1996

GBS-Syndrome

Background:
10-40% of pregnant women are colonized with Group B- Streptococci at the onset of in U.S. and Scandinavia. 50% will have perinatal transmission and 1-2% of these infants get early onset (< 7 days) neonatal infection. (Sepsis, meningitis, pneumonia). Almost all fatal cases occur within that first day of life (median age within 1 hours) mortality 5-20% and this is significantly higher in preterm infants. Neonatal symptoms: pneumonia, sepsis and meningitis, CRP increase and leucopeni. Late onset neonatal infection (sepsis, meningitis, osteomyelitis) mortality 2-6%.

Complications:
Colonization with GBS in the urogenital tract is associated with spontaneous abortion, intrauterine death, preterm delivery, preterm rupture of membranes and neonatal infection.
Maternal perinatal GBS disease include chorioamnionitis, endometritis, sepsis and UTI. Other rare maternal complications include meningitis, abdominal abscess, endocarditis and necrotizing fasciitis. There is an increased risk for endometritis and bacteremia if the delivery is by Cesarean section.
The following factors increase the risk for neonatal infection and interpartum antibiotic should be given.

- Previous child with invasive GBS infection.
- GBS bacteriuria in this pregnancy.
- Preterm birth < 37 or < 35 weeks.
- Ruptures of membranes >18 hours
- Temperature > 38^{o} C during .

The American Center for Disease suggests 2 alternative prevention strategies: (1) A risk factor approach recommending intrapartum antibiotic treatment in the above mentioned risk group (dependent on the incidence 15-20% of all pregnant were treated and about 70% cases prevented); (2) As in (1) and further low vaginal/rectal culture in 35-37 weeks and antibiotics intrapartum to all positive for GBS (dependent on the incidence this approach may prevent nearly 90% but nearly 30% will be treated).
One RTC study has found elimination of GBS in urine by giving prophylactic penicillin from 16 weeks until delivery and to decrease the risk of preterm but this has not confirmed in a larger study.
Some would give penicillin to women with a previous preterm rupture of membrane and a preterm GBS affected child but this is not evidence-based.

Culture:
Culture specimen taken both from the anal rectal region and distal part of the vagina increase the likelihood of GBS isolation. The sample should be identified for the atory as specifically for GBS culture (selective growth medium).

Treatment:
GBS in urine: penicillin po. 1 mill IE x 3 for 6 days.
During labour, 5 million Penicillin and 2.5 million every 4 hours until delivery. Ampicillin 2 gm and then 1 gm every 3-4 hours.
In case of allergy to Penicillin, Erythromycin 500 mg IV every 6 hours and/or Clindamycin 1 ½ gm every 8 hours but resistance is seen in about 10% in both drugs.
The Child: If no symptoms at birth Full evaluation and treatment less than 34 weeks.

If more than 34 weeks and mother has been treated more than 4 hours observation in 24 hours.
If more than 34 weeks and less 4 hours treatment, start treatment and further treatment dependent on blood culture, etc.

Screening Test on the Newborn:
The optimal technique for GBS screening is obtaining a single vaginal anorectal swab and use of selective growth media. The disadvantages that it requires 18-24 h before the result is available which is an issue for woman presenting in ? . For this situation two rapid antigen detection methods: Latex particle agglutination test (LPA) and enzyme-linked immunoabsorbent assay (ELISA). The sensitivity and specificity for LPA test rate from 90-91% and 93.2-99.7%, respectively. Similar for ELISA with a sensitivity and specificity vary from 74-89% and 92-100%, respectively.

References:

(1) ACOG Committee Opinion, No. 173. June 1996. Washington, D.C. American College of Obstetricians and Gynecologists.

(2) Allan MacLean, et al. Infection and Pregnancy, RCOG Press 2001.

(3) Campbell, N et al. The prevention of early-onset neonatal group B streptococcus infection: technical report from the New Zealand GBS Consensus Working Party. N Z Med J. 2004 Aug 20;117(1200):U1023

(4) Larsen JW, Sever JL. Group B Streptococcus and pregnancy: a review. Am J Obstet Gynecol 2008 Jan 15 (Epub ahead of print)

(5) www.infpregn.com

(6) www.uptodate.com 2007

HEPATITIS

Viral hepatitis does not differ from those who are non-pregnant patients except for Hepatitis E, which can be very severe.

Hepatitis A virus (HA)
Transmission: Fecal-oral. Incubations period 2-6 weeks. contagious 2 weeks before and 2 weeks after icterus 75 % of adults has symptoms.
Vertical transmission very rare with max risk for fetus near delivery if mother is contagious.
Diagnosis: Anti-HAV-IGM
Prophylaxis: 1 vaccine protect for one year. 2. vaccine given 6-12 month after the first protects in 20 years. Hepatit A vaccine (HAVRIX 1400) can be given 7 days before exposure.

Hepatitis B virus (HBV) Transmission: Parenteral, sex and vertical transmission (2-40 % after needle lesion)
Incubations period 2-6 month. contagious 4-6 weeks before icterus and 3-4 month after if not chronic infection Risk of HBV transmission is 10 times more frequent than hepatitis C and 100 times more frequent than HIV.

Acute hepatitis IgM – anti HBC:
Risk for chronic disease are > 90% in newborns and < 5% in adults. If anti HBS develop the woman is immune

HBsAg	HBV-DNA	HbeAg	anti-HBe	anti-HBs	anti-HBc	Contagiousness
+	+	+	-	-	+	Very contagious
+	-	-	+	-	+	Not very contagious
+	+	+/-	+/-	-	+	Contagious
+	+	-	+	-	+	Contagious
-	-	-	+	+	+	Previous infection, not contagious
-	.	.	.	+	-	Vaccinated

Transmission following acute HBV infection during the first trimester of pregnancy is rare unless the mother develops a persistent infection. The risk is about 6% in the 2nd trimester and rises significantly to 67% if infection is acquired on the 3rd trimester of pregnancy. The risk of mother to child transmission of HBV is strongly related to the infectivity of maternal blood.
THE CHILD is normally asymptomatic unless the mother is anti HBe pos with mutated virus in which case fulminent hepatitis can occur; Maternal-neonatal transmission usually occurs at delivery but may also be transplacental 5%.

Infection rates are highest in infants exposed to HBsAg antigen positive women who are Hepatitis B antigen (HBeAG) positive. Nearly 95% of infants born to mothers who are HBeAg positive become infected compared with 2-15% of women who are HBsAG positive but HBeAg negative. For the small number of carrier mother with HBe antibody the risk of vertical transmission is much lower, 10-20% and does not lead to chronic hepatitis B infection in those children who are infected. Neonates infected at birth have > 90% chance of becoming chronic carriers of hepatitis B with the associated risks of

subsequent cirrhosis and hepatocellular carcinoma. When a mother is found to be hepatitis B surface antigen positive, it is recommended to screen for anti HBe and antibody status.
The majority of infection is **acquired at the time of birth**. Whether the risk is higher in infant delivered vaginally than those delivered by CS section is not well established and not recommended although this has been reported in one study. Breastfeeding does not seem to be associated with an increased risk of mother to child transmission but conclusive evidence to support this is lacking. There is a 5% risk of intrauterine infection with certain genotypes. There is a theoretical risk by amniocentesis and external version, and scalp electrodes should be avoided.

Treatment of infants, (if mother is HBsAg positive) is vaccination with Hepatitis B vaccine (Engerix-B = 0,5 ml) and Hepatitis B immunoglobulin (Anautiv = 1 ml) immediately after birth, given at two different locations, at least before 24-72 hours, and can interrupt 85-99% of such mother-infant transmission.

Prophylaxis: It is recommended that newborns are given vaccination at 1, 2 and 12 months.
Hepatitis C virus (HCV)
HCV previous called non-A, non-B hepatitis. Prevalence in Denmark 0,1 - 0,5 %.
Incubation period 6-8 (2-12) weeks.

Transmission:
Parenteral, blood, IV drug users, less than 10%sexual transmitted. Risk after needle injury 3-10 %. The infection is often asymptomatic.
Milk uncommon, there appear to be only a low risk of infection with sexual contacts (< 5% of long term sexual partners get infected) or IV drug use.
Most often post-transfusion hepatitis but in many cases obscure 60-80% get chronic infection and of these 20% develop cirrhosis after 10-30 years, and 1-3% cancer.
Mother to child transmission rate is about 5-7% for HIV negative mothers and occur predominantly or exclusively in the prenatal period. The risk for HIV pos mothers 15%.
Theoretical risk for amniocentesis. Scalp electrodes should be avoided.

Diagnosis:
Chronic Anti HCV and HCV-RNA positive. Antibodies are not protective. Re-infection possible.

Treatment of chronic stage:
Not recommended in pregnancy.
There is no vaccine to prevent HCV.
Seems to be seen more often in case of intrahepatic cholestasis of pregnancy.

Hepatitis D virus
Hepatitis delta virus (HDV)
(co-infection with Hepatitis B). Transmission: Parenteral. Incubations period 3-12 weeks, Very rare in Denmark.
The risk for fulminant hepatitis is increased if the hepatitis B infection arise the same time as the hepatitis D infection
Is only found in HBsAg-positive people, most of whom are HBeAG-negative. Prevention of HBV infection or transmission will also prevent HDV. No risk for the fetus.

Hepatitis E (HEV)
Transmission: Fecal-oral, often epidemic in association with contaminated water.
Increase the risk for severe Hepatitis B infection. Incubation period 2-9 weeks. Very rare

in Denmark. Symptoms similar to hepatitis A in non-pregnant. The risk for fulminant hepatitis in pregnant woman is 15% with a mortality of 20% (hepatic encephalopathy and hepatic failure). Highest risk in III trimester. No cronic disease.

Hepatitis GBV-C
Transmission: Parenteralt does not seems to be clinical significant

Herpes simplex hepatitis (HSV) is very rare.
May cause fulminant hepatitis with an associated high mortality. Clinical signs: Fever, abdominal pain, and jaundice is unusual but transaminases elevated leucopenia and prothrombin time prolonged.

Diagnosis:
Viral culture of the liver and detection of IgG and IgM HSV antibodies may be helpful.

Therapy:
Acyclovir can also prevent/decrease transmission to the infant.
Mother to Child
Crude transmission rates have varied from 0 to 100%.

References:

Nielson-Piercy, C. Handbook of Obstetric Medicine. 2001 Edition.

(1) www. Infpreg.com

(2) www.uptodate.com 2007

Herpes

Incubation period 1-7 days shodding after primary herpes for weeks but only days after recurrence.
Pregnent women in Scandinavia: 70% HSV1 antibodies and 15-30% HSV2 antibodies.
Only 1 of 5 with Herpes type II knows they have infection.
Neonatal herpes has untreated a high mortality and morbidity with 35% risk for sequelae in survivors. The prognosis is poor even if the child is treated. In most cases of neonatal herpes, the mother has no symptoms. HSV-2 is more severe and more common than HSV-1 in the genital tract. A positive antibody titre is not protective against the other but clinical symptoms attenuated.

Definiition:

- ☐ Primary herpes - First outbreak (incubation aproximately 4 days (2-12 days)
- ☐ Non-Primary herpes - First outbreak but with anti-bodies against the other type.
- ☐ Recurrences herpes - Outbreak of herpes 1 or 2 with antibodies against the actual herpes type.
- ☐ First time herpes - First clinical observed outbreak

If the father has recurrent genital herpes and the mother has herpes negative antibodies, it is strongly advised not to have sex at the time of known recurrence - use condom in the last six weeks of pregnancy.
Shedding (primary mean 11 days, recurrent mean 4 days).

Diagnosis:
culture from lesion (ELISA, PCR) can be false negative, increase in antibodies.

Treatment:
Acyclovir - No teratogenecity found, even in first trimester.

Treatment: 1 & 2 or suspicion. Acyclovir 200 mg x 6 in 5 days.

Primary herpes within six weeks of expected date of delivery: There is 30-50% risk of neonatal herpes if the infant are delivered vaginally. Elective Cesarean section is recommended especially if no specific antibodies found. Intravenous aciclover intrapartum to the mother and subsequently to the neonate may reduce the risk.
5% risk of intrauterine infection.

Recurrent herpes at delivery has very little risk of neonatal infection and result in mild disease (0-3%). Cesarean section is recommended by some authorities if acute recurrence in the birth canal and should be performed within 4 - 6 hours after the rupture of the membrane. Some disagree with this statement and for example in the Netherlands Cesarean section has not been routinely performed for this indication since 1987 with no increase in the incidence of neonatal herpes. Some do not recommend fetal blood scalp electrode or fetal blood sampling in woman at high risk for recurrent infection (virus shedding before symptoms) and the virus can infect the brain without having contact with antibodies.

Infection in newborns Incubatintime 2-26 days and even longer if only cerebral affection.

To avoid recurrent herpes in late pregnancy, prophylaxis with 400 mg BID from 4 weeks before term.

Complications: Herpes simplex hepatitis (page 36)

References:

(1) MacLean, A., et al. Infection and Pregnancy, RCOG Press 2001

(2) Management of Genital Herpes in Pregnancy. Royal College of Obstetricians and Gynecologists. Clinical Guideline No. 30, March 2002.

(3) www.infreg.com

(4) www.uptodate.com 2007

Hydrops fetalis (nonimmune) and fetal ascites

Hydrops is excess of fluid in more than one body cavity or one exudates and subcutaneous edema.
Incidence 1/1500 to 1/4000
Appears normally in the following sequence:
Polyhydramnios, ascitis (first between bowel loops along the abdominal trunk or within the pelvis). Pleural and pericardial edema, placenta edema (> 4 cm) and edema of the skin (> 5 mm).

Pathophysiology:
Decrease plasma osmotic pressure, (lever damage or disease) increase capillary permeability (heart failure),obstruction of venous and/or lymphatic flow, and volume overload (twin-twin transfusion).

CAUSES

Hydrops
Secondary to isoimmunization (see page 82).

Non-immune Hydrops.

Genetic causes
Most common aneuploidi (10%).
Turnes Syndrome), (trisomy (21, 18 and 12) and triploidy

Cardiovascular abnormalities: 40%
Congenital heart disease
e.g. Hypoplastic left heart, AVSD and isolated ventricular and septal defect. Recurrent risk of congenital defect 2-5%.

Arrythmia: 5%
Both tachy- and bradyarrythmias
e.g. Super ventricular tachycardia or less common paroxymal tachycardia, WPS Syndrome, fetal hyperthyreodism from transplacental passage of TSH receptor stimulating antibodies, congenital block (structural and neonatal lupus, see page 65).

Vascular abnormalities
e.g. chorioangiomas of the placenta > 4 cm

Infektions
5-10% have infektions. Parvovirus B-19, Cytomegalovirus, Adenovirus, Syphilis, Coxsackievirus.
More rare: Herpes, listeria, chlamydia, rubella, respiratory syncytial virus, influenza B.

TWIN-TWIN TRANSFUSION:
10% of monochorionic twins

LUNG
5% e.g.: adenomatoid malformation, diaphragmatic hernia

INTESTINAL:
< 5%. Meconium perforation, bowel obstruction

RENAL:
< 5%. e.g. severe uropathy causing urinary ascitis.

Skeletal dysplasia:
2-5% Most syndromes have marked thoracic restriction. Over 20 types of dysplasia has been described.

Fetal akinesia syndrome:
2-3% e.g. lethal multiple pterygium syndrome, arthrogyposis multiplex congenital, Neu-Laxova syndrome, Pena-Shoiker syndrome and myotonic dystrophy.

Genetic disease:
10% Metabolic disease e.g. lysosomal storage disorders, Gaucher multiple malformation syndrome.

Fetal anemia 10-25%
(alpha-Thalasemia, red cell enzyme disorders like glucose 6 phosphatase deficiency).

Diagnosis
Maternal history, maternal blood group and antibodies screen, full blood count, Kleihauer-test, VDRL, virology (parvo-cytomegalo-adenovirus-coxsackievirus and toxoplasmosis), TORCH.
Fetal blood sampling, karyotyping, fetal blood for anemia, full blood count, blood group and direct Coombs' test, viral IgM, parvovirus, cytomegalovirus DNA karyotype.
Ultrasound scan for malformation, and Doppler middle cerebral artery for detection of severe anemia.
Amniocentesis for karyotype, cytomegalovirus DNA.
Prognosis depends on the course, if unexplained, perinatal mortality 30-90%.

Maternal complications
Mirror Syndrom refers to generalised material edema, often with pulmonary involment, that "mirrors" edema of the fetus and placenta.
May present as edema, shortness of breaths or uncontrolled hypertension with clinical presentation to that of preeclamsia (but often low hematrocit)

References:

(1) Bukowski R, Saade GR. Hydrops fetalis. Clin Perinatol 2000 Dec; 27(4):1007-31.

(2) Twining P, McHugo J, Pilling DW. Textbook of Fetal Abnormalities. Churchill Livingstone. An imprint of Harcourt Publishers Limited, 2000.

(3) www.uptodate.com 2007

Hyperemesis gravidarum

Incidence: 0.1-1% of pregnancies.

Findings:

Nausea, vomiting and there may be ptyalism (excessive salivation).
Normally from 6-16 weeks, maximum 8-12 weeks.
Severity correlated to hCG and biochemical hyperthyroidism. Weight loss > 5%.
Prefunderance of femal fetures. Conflicting evidence of the role of helicobacter pyteri
Dehydration with hyponatremia, < 120 mmol can cause seizures, spastic parous and extremely seldom respiratory failure (osmotic demyelinisation syndrome).
Hypokalemia. Metabolic hypochloremic alkalosis. Low serum urea.
Vitamin deficiencies, B12 and B6.
Mallory-Weiss tears of the esophagus and episodes of hematemesis.
Ketonuria.
Abnormal liver function test in severe cases
Abnormal thyroid function test: Increase T4 and decrease TSH but clinically euthyroid (no thyroid antibodies).T4 levels normal by 15 weeks, TSH levels remained suppressed for a longer period.
Lack of Vitamin B1 (Thiamine) can cause Werniche's encephalopathy (40% fetal loss) with abnormal ocular movements, double vision ataxsia and/or confusion, in severe cases Werniche-Korsakoff's Syndrom psychosis (only 50% is cured).

Diagnosis:

Is a diagnose of exclusion.
Other causes are most common: Urinary tract infection, peptic ulcer, pancreatitis and more rarely Addison's disease .

Treatment:

Intravenous fluid: normal saline and potassium chloride is added to the infusion bags as required (no glucose infusion)
Pyridoxin-B6 10-25 mg 3 times a day

Antihistamine H_1 receptor antagonists (Promethazine 25 mg 2-3 times a day).
Dopamine antagonists
Phenothiazines

Metoclopramid should not be used for long period as it can cause dystonia.
Serotenin 5-HT_3 antagonist: Ondansetron (Zofran) 5-hydroxytryptamin receptor antagonist 8 mg 2-3 x daily or intravenous 10 mg 3 x daily, only few studies.
Ginger 250 mg 4 times a day is more effective than placebo, but the use has recently been quistioned because of lack of evidence that Ginger is harmless in high dosis.

Corticosteroid
Methylprednisolone 16 mg 3 times a day (dose reduced by half every 3rd day), if tablet is not tolerated, hydrocortisone intravenously 100 mg BID.

Parenteral nutrition and/or enteral feeding.
Acupuncture -in PC6 and ST36mid seems very effective.
Prevention of Werniche's encephalopathy: Thiamine 50 mg 3 times a day. For severe cases intravenous treatment is required, Thiamine 100 mg diluted in 100 ml of normal saline and infused over 30-60 minutes.

References:

(1) Jewell D, Young G: Interventions for nausea and vomiting in early pregnancy. Cochrane Library. Document 1998.

(2) Nielson-Piercy, C. Handbook of Obstetric Medicine. 2001 Edition

(3) The management of Nausea and Vometing in Pregnancy SOGC Clinical Practice Guidelines N. 120 October 2002

Hypertension and preeclampsia in pregnancy

A leading cause of maternal morbidity and mortality (cerebral , adult respiratory distress syndrome, multiorgan failure, DIC), and infant mortality and morbidity and later neuro-developmental disturbances.
Occurs in 10% of pregnancies mostly primiparas.

Definitions:

- Pre-existing hypertension/chronic hypertension before 20 weeks, diastolic > 90 mmHg
- Pregnancy induced hypertension without proteinuria (gestational hypertension). Hypertension occurs after 20 weeks in a previous healthy woman and resolves by 2 weeks post partum.
- Severe hypertension: Diastolic blood pressure ≥ 110 mm Hg or systolic blood pressure ≥ 170 mm Hg.
- Pre-eclampsia- Pregnancy induced hypertension after 20 weeks with proteinuria > 0.3 g/l or 0.3 g/24 hours protein creatinine ratio 30 mg/mmol (or = 1 + on dipstick) Superimposed pre-eclampsia. Proteinuria and increase in blood pressure in a woman with existing hypertension or renal disease.
- Severe preeclampsia: Marked proteinuria > 5 g/24 hour and severe hypertension.

HELLP
Hemolysis, Elevated Liver Enzymes (AST > 70 IU/L LDH > 600 u/l). Low platelets (< 100,000µl) and elevated bilirubin > 1,2 mg/dl and may be associated with severe disseminated intravascular coagulation (DIC).

Eclampsia
Convulsion disorder in association with Proteinuric hypertension
Hypertension > 140/90 mmHg in two occasions, 6 hours apart, position lying at a 45 degree angle or sitting
Systolic Korotkoff Phase I and diastolic with Phase V (disappearance).

Risks
Previous preeclampsia
Multiple pregnancy
Underlying medical conditions: Hypertension, renal disease, proteinuria, preexisting diabetes, thrombophilia. If new hypertension before 32 weeks, 50 % risk of developing preeclampsia.

Severe preeclampsia

- > 160/110 mmHg or one or more signs or symptoms are present:
- Subjective symptoms
- Headache, visual disturbances, epigastric pain
- Clonus >= 3 beats
- ALAT (Alanine aminotransferase) > 50 u/l, transaminosis > x 2
- Elevated serum bilirubin
- Oliguria < 100 ml/hr, marked proteinuria > 5 gm/24 hours
- Serum urate > 45 mmol/l
- Serum creatinine > 110 mmol/l

- Coagulation parameters
- Thrombocytes < 100
- DIC(APTT>1.5, ATIII<70, D-dimers > 2mg/l)
- Hemolysis, LDH > 1,000, Haptoglobin < 1

A single pathological result should be evaluated with caution and if necessary be acted on immediately.
Pregnant women with a headache of sufficient severity to seek medical advice or with new epigastric pain should have their blood pressure measured and urine tested for protein, as a minimum.
Automated blood pressure recording systems can systematically underestimate blood pressure in preeclampsia to a serious degree. Blood pressure values should be compared, at the beginning of treatment, with those obtained by conventional mercing sphygmomanometers.
Women with multiple pregnancies are at increased risk of preeclampsia without proteinuria.

Differential diagnosis:
Other thrombolic microangiopathies.
Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) are often first determined when disease worsened postpartum. HUS mainly affects the kidneys and in TTP neurological abnormalities are dominant. However many patients present with severe neurological abnormalities such as seizures and coma together with acut renal faiture. These patients can best be described by the comprehensive term TTP-HUS.
TTP is associated with platelet aggregation leading to thrombocytopenia
There is a widespread organ damage but mainly symptoms from CNS. TTP is diagnosed by the classic pentaed: thrombocytopenia (often with purpura but not usually severe bleeding), microangiopathic hemolytic anemia (blood smear with marked blood cell fragmentation ~ helmet cells and microspherocytosis), fever, renal and neurologic symptoms, elevated LDH with normal coagulation status. Heart failure ADAMS 13 deficiency.
The treatment of both TTP and HUS include supportive measures and plasma exchange transfusion (beginning with 40 ml/kg fresh frozen plasma). Corticoid can be given with reported response rate about 30%.
HELLP affects mainly the liver with elevated liver enzymes and anemia as a late symptom.
Acute fatty liver of pregnancy may be a variant of preeclampsia. There is often profound hypoglycemia and marked hyperuricemia. serum aminotransferase from moderate up to 1000 IE/L Thrombocytopenia less pronounced and white blood count more elevated. There is often marked hypertension and proteinuria despite marked elevated liver enzymes.
Lupus syndrome: Primary DNA antibodies, cellular cast in urine, decrease in complement factorsand increased split products (see page 63).

Prevention:
Low dose aspirin and calcium supplementation appear to reduce the risks of hypertension in pregnancy and of preeclampsia, especially in women at high risk.
Either agent may be used as attempted prophylaxis for women considered to be at high risk of hypertensive disorders. (75 mg aspirin or 500 mg calcium carbonate daily, commenced after the first trimester appear to be appropriate doses). Grade A.

Maternal Risk
Severe hypertension: Diastolic blood pressure greater than 110 mmHg (cerebral

bleeding).
Eclampsia or symptoms of imminent eclampsia (aspiration, Cerebral insults).
Renal impairment: rising urea/creatinine/ oliguria
Rapidly progressive non-dependent edema
Pulmonary edema
HELLP syndrome
DIC

Fetal Risks:
The risk of impaired fetal wellbeing Ssignificant intrauterine growth retardation and abruption.

MANAGEMENT OF PRE-EXISTING HYPERTENSION IN PREGNANCY

Woman on medication can often reduce their dose or discontinue medicine in early pregnancy.
Woman on angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers should discontinue them, as these drugs are teratogenic and may cause oligohydramnios, pulmonary hypoplasia, renal failure, renal tubular dysgenesis and hypotension and decrease skull ossification (hypocalvaria) and there is also a risk of intrauterine fetal death.
The beta-blocker atenolol may be associated with growth restrictions and is not recommended for use in pregnancy.

MANAGEMENT OF HYPERTENSION AND SLIGHT TO MODERATE PREECALMPSIA

NOTE: MILD TO MODERATE HYPERTENSION OR PROTEINURIA ON THEIR OWN DO NOT IMPLY ANY RISK TO THE MOTHER; THEY ARE MERELY MARKERS OF THE DISEASE NOT NECESSARILY AN INDICATION FOR INTERVENTION.
Women with hypertension and mild preeclampsia may be managed as an outpatient. If diastolic blood pressure = 100, Proteinuria < 1.5 gm/24 hr (= 2+) and no subjective symptoms, and only slight effect on biochemical test.
Blood pressure and urinalysis twice weekly.
Biochemical test weekly (serum urea, creatinine, uric acid, haemoglobin, platelet, liver function test).
Test of fetal well being with Doppler, amniotic fluid index and eventually CTG weekly
Biometry of the fetus every second week
Timing of Delivery: Slight to moderate preeclampsia Induction at 37-38 weeks or consider induction at term.
Chronical hypertension induction at term

Antihypertensive Treatment:
Antihypertensive drug treatment is not usually indicated for women with nonproteinuric gestational hypertension.
However, a diastolic BP > 105 mmHg represents an appropriate level at which to initiate anti-hypertensive therapy as protection against intracerebral hemorrhage.
A lower threshold may be considered where the disease has arisen at < 28 gestation.
On those rare occasions when an antihypertensive agent is indicated for mild gestational hypertension the choic of drug should be governed by the clinician's experience and the woman's preference. Appropriate first-line choices include the alpha agonist, methyldopa or the beta blocker, labetalol. There is little good evidence that one antihypertensive is better than another.

Drugs
Methyldopa is the drug of choice in pregnancy as it has been extensively studied. It has side effects including depression, sedation and postural hypotension.
Maximum plasma concentration after 3-6 hours and maximum effects after 24 to 48 hours
Dose: 250 mg X 3 to max 500 mg x 4.
Cave: Leverinsufficiens

Labetalol max plasma concentration after 1-2 hours, effect after ½ hours. Dose: 200 mg x 3 to max 300 mg x 4. Cave asthma,
Acute therapy: begin with IV 20 mg followed at 10 minuts interval by dosis of 20 to 80 mg 40 mg then 80 mg up to a maximum cumulative dose of 300 mg. The fall in blood pressure begins within 5-10 minuts and last from 3 to 6 hours.

Nifedipine (Adalat) should be given orally not sublinqvaly as it can cause severe hypotension. The fall begins within 5 to 10 minuts and last from 3 to 6 hours.(max plasma concentration after 30-60 min). Dose: 10 mg x 2 max 30 mg x 3. Can cause headache.

Hydralacin: Dose 5 mg IV over one to two minuts repeated bolus 5-10 mg depending upon initial respons evey 20 minuts to a maximum cumulative dose of 20 mg.
Cave: The fall in blood pressure begins within 10-30 minuts and last from two to four hours.

Magnesium Sulphate: (see contraindication)

Loading dose 4 gms mixed with 50 mls of IV fluid (D5W, NS, LR, etc.) slowly over 10 min period followed by a maintenance infusion of 1 g/hr mantained for 24 hours after the last seizure.
Recurrent seizure should be treated with either a further bolus of 2 g magnesium sulphate or an increase in the infusion rate to 1,5 to 2,0 g/hour.
Magnesium toxically do not need to be monitored routinely and toxic can be clinical assed by clinical assement by loos of Patellar reflexes and respiratory depression.
Calcium gluconate 1 g over 10 minuts can be given if there is concern about respiratory depression.

Monitoring Serum Levels of Magnesium is seldom indicated.
In case of fast treatment of hypertension – hydralacin iv or im or labetelalol oraly or IV nifedepine oraly not subligually

Contraindication:
Serious impaired renal function se-creatinine > 300mmol/l cardiac disease especially atrioventricular block. Myastemia gravis, respiratory paralysis.

Care:
Adalat and MgSO4 should not be given together (cardiotoxity) and can cause hypotension (risk for AMI)

Therapeutic range level 6-8 mg/l or 2-3.5 (4) mmol/l.
Magnesium Blood Levels:

1.8 mg (.75-1.25 mmol)	- Normal
4.8 mg (1.65-3.3 mmol)	- Therapeutic for seizure prophylaxis
10-12 mg (4.1-4.9 mmol)	- Loss of knee jerk
12-15 mg (4.9-6.2 mmol)	- Respiratory failure
> 15 mg (6.2 mmol)	- Cardiac arrest

MANAGEMENT OF SEVERE HYPERTENSION, PREECLAMPSIA AND HELLP

Severe hypertension is conformed with a diastolic blood pressure ≥ 110 mm Hg (Korotkoff phase 5) or a systolic blood pressure ≥ 170 mm Hg on two occasions and that together with significant proteinurea (at least 1 g/L ~ 2+.
An important variant is HELLP syndrome (haemolysis, elevated liver encymes and low plateled count).

Clinical fetures

Severe headache, visual disturbances, epigastric pain and or vomiting, liver tenderness, sign of clones, platelet below 100 abnormal liver enzymes (ALT or AST) rising above 70 IE/L. If > 150 IE/L it associated with increased morbidity to the mother.
Because of high false positive rate with dipsticks, 24 hour urine collection is recommended to confirm significant proteinuria.

There is an increased capillary permeability (low albumin).
Combined with increased vascular resistance with high pulmonary wedge pressure results in increased risk of pulmonary edema.

Steroids are given before 34 weeks for fetal lung maturity (for HELLP se later).

Induction/Cesarean section especially after 32 weeks when patient has stabilized.

If blood pressure is less than 160/110 mmHg, and no other signs appear, immediate delivery is not indicated, but in case of:

- Maternal symptoms, e.g. severe headache, epigastric pain
- Eclampsia
- Rapidly worsening biochemistry/hematology.

Fetal consequences:

- Fetal distress: (biophysical profile and CTG)
- Severe intrauterine growth retardation
- Absent or reverse diastolic flow in umbilical artery
- Brain sparring

Monitoring

Full blood count, urea, creatinine, electrolytes, liver function test, uric acids, DIC test, urinary output
Half hourly pressure recording and after each dose of hypertensive given
Early use of invasive monitoring if satisfactory response on treatment.

Women who had early severe preeclampsia or preeclampsia associated with fetal growth restriction, stillbirth or abruption, may be

tested for thrombophilia.

High dose Glucocorticoid Therapy to improve laboratory abnormalities in patients with HELLP syndrome.

For most patients with HELLP syndrome, 10 mg intravenous dexamethasone every 6 hours for 2 doses followed by 6 mg intravenous dexamethasone every 6 hours for 3 additional doses.

For selected patients at highest risk, include those with profound thrombocytopenia (<20,000 mm^3) or with central nervous system dysfunction (ie, blindness, paralysis) 20 mg intravenous dexamethasone every 6 hours for up to 4 doses)

MANAGEMENT OF SEVERE HYPERTENSION (> 160/110 mmHg)

Fluid Balance Management

- Fluid intake should be restricted to 80 ml/hour. Over infusion increases the risk of pulmonary edema.
- Urinary output should be measured hourly.
- 500 ml human albumin solution (HAS) should be considered:
  - prior to hydralazine therapy
  - prior to Cesarean section
  - if oliguria is evident (defined as urinary output less than 100 ml in a consecutive four-hour period)
  - prior to the administration of regional anaesthesia
- If the central venous pressure value is greater than 10 mmHg, 20 mg Furosemide should be considered.
- If the central venous pressure value is less than 0.5 mmHg, HAS 500 ml should be considered.
- A further dose of 20-40 mg Furosemide should be considered if there is persistent oliguria.
- In case of severe preeclampsia (significant symptoms rapidly progressing and hypereflexia) or eclampsia give MgSO4.

  Antihypertensive therapy should be used for pregnant women with severe hypertension for maternal benefit. The exact level at which to institute antihypertensive treatment is controversial.

  Most will treat $\geq$ 160 systolic and $\geq$ 100 diastolic (or $\geq$ 110)

  The target blood pressure is diastolic 95-105 mmHg, e.g. 150/100 mmHg.

Overzealous control runs the risk of jeopardizing the uteroplacental circulation and causing IUGR.

Use oral treatment if possible and avoid drastic reduction in blood pressure.

TREATMENT OF ECLAMPSIA

In UK 1/3 of women with ecllampsia had maximal diastolic blood pressure of ≤ 100 mmHg

Maintain airway, avoid aspiration, administer oxygen.
Arrest seizures: magnesium sulphate and diazepam, if the fit continue.
Seizure prophylaxis: Magnesium sulphate
Antihypertensive therapy

Monitoring: half hourly BP (Dinamap, if available) but control with manuel recording, ½ houry pulse and urine output hourly neurological assessment serum Magnesium if indicated. If eclamptic patient is unconscious for more than 30 minutes or have focal neurological symptoms, the patient should be referred for medical opinion and CT scan**.**

DURING LABOUR

Regional anesthesia:

Should be encouraged as it also helps to control hypertension and avoid fluctuation in blood pressure associated with regional anesthesia and intubation. Most anesthetist used a cut off for platelet count of 60-70 (80 in UK)

Ergometrin: Should be avoided because it cause an acute rise in blood pressure

Treatment of Seizures: See Eclampsia/magnesium sulphate

The preeclamptic patient is dehydrated with intravascular volume, volume depletion, with increased intestitial volume. After delivery fluid is going from intestitial tissue to the intracellular and intravascular tissue with a further risk of pulmonary edema and cardiac decompensation. The patient should not receive more than 500 ml of saline if not bleeding without knowledge of the central venous pressure. Right atrial pressure (specially normal and high by CVP) may not always accurately reflect left atrial pressure and a pulmonary artery catheter (Swan Ganz Catheter) may occasionally be indicated. Basal fluid regimen 85-100 ml NaCl/hour.

Oliguria is common.
Diuretics are usually inappropriate in the management of postpartum oliguria unless there is obvious signs of fluid overload or pulmonary edema.

Treatment of long standing oliguria (> 6 hours urinary output < 30 ml/per hour) or < 0.5 ml/kg/hour. If CVP < 5 mm albumin, Hg 250-750 ml NaCl. If CVP > 5 and no effect of diuretics, Dopamine 1-5μg/kg/min IV.

Treatment of postpartum hypertension is common and often not anticipated.
The blood pressure rise after normal delivery and reach a peak 3-4 days postpartum.

Eclampsia is a risk for the first 48 hours after delivery, but can occur up to 7 days after delivery.

Antihypertensive drugs can always be discontinued after 2-3 days if blood pressure < 110 diastolic.

Methyldopa should be avoided post partum because of its tendency to cause depression.

ACE inhibitors and Angiotensin II receptor blockers may safely be used postpartum.

It is possible to switch to the patient's previous anti-hypertensive regime after delivery.

PROPHYLAXIS

Prophylaxis:

In patients with previous preeclampsia, the risk of recurrence is 15%.
If the woman's mother had preeclampsia and the sister has a history of preeclampsia, the risk is about 25%.
Examined for thrombophilia.
If abnormal uterine artery Doppler recording (Notch) are noted, the risk is further increased.

Medication:

Low dose aspirin 75 mg/day, Started before < 16 weeks, decrease the risk by 15% both in woman at high and low risk.

Calcium gluconate 1 g daily has been shown effective in some studies.

Folic acids 5 mg daily especially in women with a high level of homocystein.

Anti-oxidants:

- Vitamin C 1,000 mg/day
- Vitamin E 400 iu/day

Promising in some and doubtful in other studies.

References:

(1) Fontenot MT et al. A prospective randomized trial of magnesium sulfate in severe preeclampsia: Use of diuresis as a clinical parameter to determine the duration of postpartum therapy. AMJOG. 2005, vol 192, number 6, 1793-94

(2) Nelson-Piercy C. Handbook of Obstetric Medicine. Second Edition, By Martin Dunitz, Ltd., published in the United Kingdom in 2002.

(3) Sibai, MB, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol 2007;196:514,e1-514,e9

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(5) www.uptodate.com 2007

INDUCTION OF LABOUR

Indication is made once a continuation of pregnancy might impair risk for mother and/or fetus and there is no contraindication for vaginal delivery. The pregnancy should end within a reasonable time, if not, normally Cesarean section should be performed.

Indication:

- In normal pregnancies after 41 weeks. Some (Denmark) recommend 42 weeks. This routine induction of labour at 42 weeks has recently been questioned in a readable article. SM Menticoglou, PF Hall, 2002.
- Severe hypertension, (systolic: ≥ 170 – diastolic: ≥ 110)
- Diabetes prior to the estimated date of delivery.
- Abruptio and/or fetal distress in case Cesarean section are not indicated.
- Intrauterine growth retardation.
- Pre- rupture of membranes after 34 weeks.
- Isoimmunization
- Chorioamnionitis
- Intrauterine death (coagulopathy first after more than 4 weeks)

Contraindications:

- Severe fetal distress
- Placenta or vasa praevia
- Previous uterine surgery, myomectomy in case the uterine cavity has been opened
- Classical uterine incission
- Feto-pelvic disproportion
- Grand multipara is a relative contraindication
- Transvere lie
- Previous Cesarean section more than 1. In selected cases, woman can deliver after 2 previous Cesarean section.
- Some maternal cardiac conditions

Risks:

- Tonic contraction
- Hypertonus
- Fetal distress especially in compromised fetu**s**
- Uterine rupture (multiparas, scarred, titanic contraction)
- Water intoxication**.**

Induction: Fetal wellbeing should be controlled prior to induction

Care During:

Continuous electronic fetal monitoring during oxytocin infusion, and after prostaglandin contraction.
Uterine hyper-contractility: Single contraction lasting < > 2 minutes or contraction frequency of 5 or more in 10 minutes.
Oxytocin should be decreased or discontinued.

Uterine tocolysis should be considered especially in the presence of abnormal fetal heart rate (FHR).
Suggested regime is subcutaneous Terbutaline 0.25 mg or Nitroglycerin resoriblet 0,25 mg or 0,4 mg sublingual or as nasal spray as required.
Possible soon delivery, eventually by Cesarean section.

Methods of Induction:

Prior to formal induction of labour, women should be offered sweeping of the membranes which reduce duration of pregnancy with 3 days. (increase level of discomfort, no increase of infection risk, and may facilitate the induction).

Prostaglandin should be used in preference to Oxytocin when induction is undertaken with intact membrane regardless of the cervical favorability.

Either Oxytocin or Prostaglandin (PG) may be used when induction of is undertaken in women who have rupture of membranes, as they are equally effective.
Intravaginal Prostaglin E_2 seems to be as effective as intracervical Prostaglandin but less invasive. Uterine hyper-contractility with a fetal heart rate is reduced with the use of vaginal gel formulation in comparison with suppositories but they are equal effective.

Prostaglin E_2 in sustained released form, should be removed at the onset of hyper stimulation.

Vaginal Prostaglandin 3 mg PGE2, 6-8 hourly, maximum doses 2 tablets for all women.

PGE2 gels, 2 mg PGE2 for nulliparous with Bishop <4,(see later) all other patients 1 mg dose to be repeated 6 hours later. Maximum dose 4 mg PGE2. For nulliparous women with an unfavorable cervix and 3 mg for all other women.

Misoprostol (PGE1) 25 mg repeated after 6 hours has been reported superior or as effective as PGE2 gel. Doses up to 25 mg 4 hours up to 6 times has been reported. Because of lack of experience many do not use it in case of previous Cesarean section.

Comparing misoprostol 50 µg and 25 µg there seems to be more hyperstimulation and Cesarean section (C/S) caused by fetal distress but less C/S because of dystocia, less intrusmental vaginal delivery and sphicterupture than in the low dose regime.

A recently study has shown that titrated oral misoprostol was associated with a lower incidence of uterine hyperstimulation and lower Caesarian delivery rate than vaginal misoprostol 25 mg every 4 hour for induction in women with unfavourable cervix. Misoprostol was given as 20 mg per hour in the first 4 hours. After 4 hours the dose was increased to 40 mg and after further 4 hours the dose was increased to 60 mg.

Oxytocin (in the presence Oxytocin should not be started before 4-6 hours following PGE2 administration or 30-60 minutes after removal of Prostaglandin in sustained-release form.

Induction with Oxytocin:
Treatment Regimes:

- 30 iu in 500 ml normal saline; hence 1 ml/hr = 1 milliunits oxytocin per minut.
- 10 iu oxytocin in 500 ml of normal saline; hence 3 ml/hr = 1 miliunits oxytocin per minute

Oxytocin is delivered through an infusion pump via a syringe driver with a non-return valve.
Oxytocin performance is optimized with ruptured membranes.

Time after Starting (minutes)	Dose Oxcytocin infusion (milliunits/ minute)
0	1
30	2
60	4
90	8
120	12
150	16
180	20
210	24
240	28
270	32

Most women should have adequate contractions at 12 milliunits per minute.

Doses up to 32 milliunits per minute should not be exceeded.
Maximum licensed dose is 20 milliunits per minute.
If regular contraction not established after TOTAL of 5 iu (five hours on suggested Regimen) then induction should be stopped.

Ballon catheter: Foley catheter No. 16 with the tip removed and 30 to 80 ml ballon through the internal os into the extraamniotic apace. The ballon installed with Saline and retracted to it rest against the internal os.
A double ballon 80 ml x 2 are also developed.
In a smal study it was more succesfull than prostaglandin and oxytocin.

Modified Bishop's score

Cervical feature	Pelvic score			
	0	1	2	3
Dilatation (cm)	< 1	1-2	2-4	>4
Length of cervix (cm)	> 4	2-4	1-2	<1
Station (relative to ischial spines)	-3	-2	-1/0	+1/+2
Consistency	Firm	Average	Soft	-
Position	Posterior	Mid/Anterior	-	-

References:

(1) Andresen DM, Jensen JS, Ulbjerg N. Misoprostol-a safe preparation for induction of labour. Ugeskr Laeger, 206 Oct 23;168(43): 3711-4.

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(5) Savas M. Menticoglou, Philip F. Hall. Routine induction of at 41 weeks gestation: nonsensus consensus. British Journal of Obstetrics and Gynecology 2002; 109:485-491.

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INTRAUTERINE GROWTH RESTRICTION (IUGR)

Definition: A fetus that has not reached its growth potential.
Small for gestational age (SGA) refer to fetal weight deviation in percent of standard deviation in relation to growth curve. Normally defined as below the 10 centile (86 % of median weight).
SGA includes IUGR and constitutionally small fetus (50-70% of SGA below 10% percentil).
The lower the birthweight centile, the higher the risk of intrauterine growth restriction = intrauterine growth retardation.

Traditionally divided into in:
Type I symmetrical 20%
Type II asymmetrical 80%

Biometrical test: Test to meassure size
Biophysical test: Test to assess fetal well-being

Birthweight for Gestational Age

Week 26+0	30 + 0	34 + 0	38 + 0	40 + 0	42 + 0	Gestational Age
950	1600	2380	3200	3600	3900	Expected weight
740	*1250*	*1850*	*2500*	*2800*	*3100*	*-22% weight deviation ≈2 SD*
620	*1050*	*1550*	*2100*	*2320*	*2550*	*-35% weight deviation ≈3 SD*

10% percentile ~ ca. 15% weight deviation
5% percentile ~ 18% weight deviation
2,3% percentile ~ 2 SD ~ 22% pre-SD
1% percentile ~ 28% weight deviation
0,1% percentile ~ 37% weight deviation

Causes and risk of IUGR:
(1) Previous IUGR
(2) More than two spontaneous abortions
(3) Fetal Factors:
- Karyotype abnormalities. This figure is higher if severe IUGR and if structural defects, normal liquor volume and normal uterine and umbilical artery Doppler flow are seen.
- placental mosaicism
- genetic syndrome
- major congenital abnormalities
- multiple gestation

(4) Fetal Infections
Virus:
- CMV
- Rubella
- Varicella

Protozoa:
- Toxoplasmo
- Malaria

(5) Bacterial:
- Listeriosis

(6) Placental Factors:
- Placental injuries, mosaicism and abruption
- Thrombophilia related uteroplacental abnormalities
- Chronic inflammation

(7) Gross placental structure anomalies
- Velamentorus insertion of umbilical artery
- Chorioangioma
- Single umbilical artery
- Bilobate placenta
- Placenta previa

(8) Maternal Factors: Medical disorders:
- Preeclampsia
- Collagen/Vascular disease
- Thrombophilia
- Antiphospholipid syndrome
- Renal disease, Myxoedem, anemia

(9) Medications:
- Abuse (Smoking, Alcohol)
- Toxic Antineoplastic)

(10) Low calorie intake:
- Famine example under World War II ≈ the birth weight was decreased by avarage 500 g in Stalingrad.
-

(11) Maternal Hypoxemia:
- Anemia
- Cyanotic heart disease
- Chronic pulmonary disease
- High attitude: 65 g for each 500 m above 2000 m

Complications of IUGR:
Fetal distress, Hypoxia, Acidosis and Low Apgar Score at birth.
Increased perinatal morbidity and mortality
Grade 3-4 intraventricular haemorrhage
Necrotizing enterocolitis
Bronchopulmonary dysplasia
Metabolic disturbances and hypoglycemia
Polycytemia
Hypothermia
Impaired cognitive function and cerebral paresis.

Measurements of fetal growth:
Symphysis – fundal distance (SF) in early studies reported sensivities of 56-86% and specificities of 80-93%. Seems best to predict early severe cases as both fetal weight and amnotic fluid decreases. However the impact of SF is uncertain.

Estimation of fetal weight by ultrasound.

In 5% of fetal weight estimation the real weight deviate > 14%.
Fetal wellbeing: movements by the mother.
CTG.
Doppler flow and biophysical profile.

The risk of IUGR in patients with chronic hypertension increase with abnormal uterine notch. Growth is more important than size in predicting poor fetal outcome AC growth < 40 mm in 2 weeks are abnormal.

Doppler:
Use of Doppler in IUGR are associated with a reduction in perinatal death and induction of labour and less emergency Cesarean sections (Cochrane).

Flow in uterine artery.
Increased flow especially in third trimester increases the risk for repeat IUGR and preeclampsia. The sensitivity is higher in II trimester than in I trimester. If normal at 22-24 weeks no further control seems indicated.
Uterin artery score:

0 Normal bilateral flow
1 One abnormal parameter Pulsatility Index (PI) in II trimester > 1,2 or notch
2 Two abnormal parameters
3 Three abnormal parameters
4 Four abnormal parameters

The parameters could be either high pulsatility index and or notch

Sequence of Doppler changes in severe IUGR < 32 weeks.

Early stage: Mild to moderate

Redistribution.

- MCA (Middle Cerebral Artery). Pulsatility Index decreases
- UA (Umbilical Artery) pulsatility index increases

Amniotic fluid drops.
Umbilical artery end diastolic flow disappears = absent end diastolic flow (AEDF)
Aorta pulsatility index increases (reduced short term variability) .

Late Stage:

- Decreased or reversed flow in ductus venous during late diastole
- UA (Umbilical Artery) Reverse flow (RF), Aorta reverse flow
- Ductus venosus reverse flow and vein pulsation in umbilical vein and inferior vena cava .

Some believe that fetal heart rate changes are late signs of fetal distress and believe venous Doppler changes comes early in the decompensated phase.

<u>IUGR < 32-34 weeks</u> umbilical artery Doppler and other fetal Doppler measurement may help in timing the delivery in cases of severe IUGR at early gestational age, but is proven more useful in a context of serial measurements.

Do not consider delivery if there is normal umbilical artery flow, fetal movements and normal amnotic fluid.

Deliver if CTG shows late deceleration,
Abnormal venous flow 2-3 SD
Reversed EDF by 31 weeks
Absent in diastolic flow by 33 weeks
Reduced EDF by 36 weeks
Remember antenatal steriods before 34-(36) weeks

Antenatal surveillance in gestational age < 32-34 weeks is unnecessary in fetus suspected for IUGR if umbilical artery Doppler is normal and fetal movement is registered by the mother and there is normal amount of amniotic fluid.

In preterm IUGR, absent or reversed umbilical artery blood flow (UA-AREDV) is strongly associated to perinatal mortality and acidosis: Ductus venosus Doppler most effectively identifies those preterm IUGR that are at higher risk of adverse neonatal outcome (particularly stillbirth) at least one week before delivery. Based on present observation a cut of value for ductus venosus flow of 2-3 SD seems to be most appropriate for delivery of GA below 30 weeks.

Absent or reversal of arterial velocity in the ductus venosus and pulsation in the umbilical vein have a high specificity [98%] and positive predictive value [82%].

Thus in very preterm IUGR fetuses an important intrauterine time can sometime be gained if venous flows are normal. However, only 50% of fetuses at risk for audosis develop abnormal venous flow. Therefore, additional tests like computerized cardiotocography and biophysical profile score are of value.

In case of abnormal umbilical flow 2 and 3, and brain sparring (MCA > 2 SD), biophysical profile do not add to outcome prediction.

Dilemma:
Waiting for these changes can cause intrauterine fetal deaths and neuro-developmental damage but this can also be caused by early preterm delivery itself.

Spontaneous late decelerations often coincides with pulsation in the umbilical vein or abnormal ductus venosus flow.

50% of the fetuses seem to have abnormal fetal heart rate before venous Doppler changes. Uterine artery notch increases the risk.

IUGR > 34-36 weeks

If IUGR (≥ 36 weeks < 5 percentile ~ 18% weight donation): Delivery.

Umbilical Doppler > 32 weeks is not necessarily reassuring.

SGA fetuses with normal umbilical artery and abnormal uterine and/or fetal middle cerebral artery waveforms have an increased risk of fetal distress and being

delivered by Cesarean section

Deliver if in doubt
- No growth in 2-3 weeks
- CTG no acceleration

Normal biophysical profile (BPP), false negative stillbirth rate of 0.1 per 1,000 within 7 days.

Amniotic fluid index < 5^{th} centile or ≤ 5 cm, a single cord-free pocket depth (< 1 cm, 2 x 1 cm, 2 x 2 cm) have all similar diagnostic accuracy, good negative predictive value in high risk pregnancies and are rarely abnormal, when Doppler findings are normal.

Change in biophysical profile
(1) Decreased variability
(2) No breathing movements
(3) Decline in amniotic fluid
(4) Loss of movement and tone

Abnormal Biophysical Profile and Doppler cerebral/umbilical ratio are associated with low umbilical artery pH, low apgar score and increased rate of Cesarean section.

Abnormal Doppler findings normally precedes abnormal biophysical profile.

Action Plan In Case of IUGR

Weight Deviation	25(0) – 31(6)	32(0) – 36(6)	37(0)+ weeks
-15% to -21%	US /2-3 weeks	US/2-3 weeks	US:/2-3 weeks or delivery
-22% to -34%	US: weekly Doppler: AED C/S, but especially < 28 weeks followed by CTG and Doppler daily and BPP twice weekly. Reverse diastolic flow, late deceleration and pulsative venous flow: C/S	US: weekly Oligo & reverse diastolic flow:C/S AED: daily CTG, Doppler, weekly BPP If Deterioration, C/S	Consider delivery If Doppler, CTG, BPP normal control 1 x 2 weekly, if AED/oligo/ NST nonreac-tive/ BPP ≤ 6:delivery
≥-35%	Karyotype (especially if normal flow and amniotic fluid). Antiphospholipids (APS), ANA, infections (TORCH), thrombophillia. If ANA and APS high levels consider heparin. Doppler: AED C/S but especially < 28 weeks followed by NST, and Doppler daily and BPP twice weekly. Reverse diastolic flow, late deceleration and pulsative venous flow: C/S.	Karyotype (especially if normal flow and amniotic fluid). Antiphospholipids (APS), ANA, infections (TORCH), thrombophillia. If ANA and APS high levels consider heparin. AED: C/S Increase P1 consider delivery even if NST and BPP normal.	Delivery. AED: C/S

AED: absent and diastolic flow in umbilical artery. BPP: Biophysical profile.

Rules of Thumb for the Prognosis in Preterm Infants							
Gestational age	24	25	26	27	28	29	32
Survival	40%	50%	60%	70%	80%	90%	>97%
Normal among survivors	40%	50%	60%	70%	80%	90%	>97%
Celeston & surfactant	The prognose 1-2 weeks better than gestational age						
<85% of median weight	The prognose 1 week worser than gestational age						
<75% of median weight	The prognose 2 weeks worser than gestational age						

Prognosis for live born without abnormalities (ETFOL)		
Gestational age	Survival rate	Live born without severe handicaps
24	33%	75%
25	58%	82%
26	67%	84%
27	79%	87%

Association between gestational age and survival as well as survival with or without handicaps. Summery of Sandbjerg Guidelines			
Gestational age	Survivals, born after 1990	Severe handicaps*	Mild handicaps/ cognitive problems*
</=24	35%	11-79%	22-72%
25	70%	30%	7-53%
26	70%	10%	30%
27	80%	10%	
28	80%	5%	
29-30	90%	4%	
31-32	93%	7%	
33-34			
35-36			

*: Percent of survivals

Prognosis without consideration to gestational age (GRIT 1999)			
	Neonatal mortality	Severe handicaps at 2 year examination	Dead or severe handicaps at the age of two
Flow class 1	5%	4%	11%
Flow class 2	15%	9%	25%
Flow class 3	30%	16%	38%

GRIT (Steve Thornton, presented at Course of fetal medicine, London 1999)

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6) Habek D, Herman R. Fetal biophysical profile and cerebro-umbilical ratio in assessment of perinatal outcome in growth-restricted fetuses. Fetal Diagn Ther 2007;22(6):452

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8) Severi FM, Bocchi C, Visentin A, Falco P, Cobellis L, Florio P, Zagonari S, Pilu G. Uterine and fetal cerebral Doppler predict the outcome of third-trimester small-for-gestational age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol 2002 Mar;19(3):225-8.

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LUPUS ERYTHEMATOSUS (SLE)

SLE is a chronic autoimmune systemic inflammatory connective disease characterized by periods of tissue disease activity (flares) and remission with a variety of clinical and antibody patterns.

Clinical Features:

Joint involvement is common (90%) but also skin (butterfly rash), Raynaud phenomen, renal (glomerulonephritis), pleuritis, pericarditis and hematological manifestations including hemolytic anemia, thrombocytopenia, lymphopenia, or leukopenia are common.

Antiphospholipid antibodies (aPL) are found in 50% of patients, being itself not diagnostic for antiphospholipid syndrome (APS) without clinical manifestation but it increases the risk of thrombosis and 50% develops APS in the future. The principal aPL are anticardiolipin and lupus anticoagulans.

Antibodies: ANA is found in 98% of SLE patients, 96% sensitivity and specificity. ANA is good for screening but is not enough for the diagnosis. DNA are the most specific (78% of patients) and the DNA level is associated with the activity of the disease. They may also have antibodies against extractable nuclear antigens, for example cytoplasmic ribonucleoproteins, anti RO/SSA (30% of SLE) and anti LA/SSB or to phospholipids, i.e. anticardiolipin and lupus anticoagulant (50% of patients). 0,5% prevalence anti RO/SSA in asympthomatic pregnancie.

Lupus nephritis: Risk of deterioration is greater, the higher the baseline serum creatinine.
Woman should avoid pregnancy for 6 months after a lupus nephritis flare.

Risk: Spontaneous miscarriage 20%, fetal death, preeclampsia, and intrauterine growth retardation 45% and preterm delivery 45% are related, anticardiolipin antibodies, lupus anticoagulant, lupus nephritis or hypertension or active disease.

Exacerbation of SLE (Flares) occur in up to 60% of pregnancies but better management with use of steroids may have decreased this percentage.

Risk of preeclampsia especially early in pregnancy.
Pregnancy in women with lupus nephritis is associated with an increase risk of fetal loss (up to 75%) and worsning of renal and extrarenal manifestations.

Monitoring: Blood pressure, renal function, blood count and RO/SSA and anti La/SSB antibodies, LA and aCL assay, anti DNA-antibodies complement (CH50 or C3 and C4)

Management: Flares must be actively managed. NSAID and Aspirin can interfere with implantation. The woman should receive profylatic Heparin and 75 mg Aspirin if she has antiphosfolipid syndrome to prevent pregnancy loss.

Corticosteroids are the drugs of choice. Prednison, and metylprednisolon cross the placenta at very low concentration, whereas dexamethason and betametason reach the fetus in higher concentrations.
Azathioprine may be used very cautiously. Cyclophosphamide and Methotrexate should be avoided, because of a high risk of causing birth defects. Antimalaria drugs is probably safe. Hydroxychloroquine should not be stopped as it may precipitate flares.

Differential: Diagnosis: Preeclampsia, lupus nephritis is often associated with proteinuria and/or active urine sediment. Lupus has rising anti-DNA antibodies and red blood cells or cellular casts in urine. A fall in complement levels and increase in complement split products particularly Ba and Bb. High rate of CH50/Ba may thus differentiate preeclampsia from those with active lupus as complement are usually but not always increased in pregnancy.

In preeclampsia, there are more common thrombocytopenia, elevated liver enzymes and uric acid.

Preeclampsia with SLE called superimposed preeclampsia (SLE (15%) are more likely to develop renal function, abnormal liver dysfunction and hyperuricemia.

LUPUS SYNDROME (NEONATAL)

Neonatal lupus is a passively transferred autoimmune disease that occurs in about 1-2 percent of babies born to mother with autoimmune disorders including SLE, Sjoegrens syndrome and to women with antibodies against Ro/SSA and La/SSB in the absence of autoimmune disease. Neonatal lupus are caused by passage of the anti-RO/SSA and/or anti-LA/SSB from mother to child after the 20 week of pregnancy

CUTANEOUS MANIFESTATION: 5%-10%.

Recurrence: 15-25%.

Manifestations:
Usually it manifests in the first 2 weeks of life, [erythromatous anular lesions or arcuale macules] located primarily on the scalp and periorbital area] disappears spontaneously within 6 months but hypo-pigmentation and telangiecstasia may persist up to 2 years. Hematologic manifestations such as thrombocytopenia and congenital heart block may occasionally occurs. Sunlight should be avoided.

Most symptoms resolve within few months.

CONGENITAL HEART BLOCK (CHB) IN ONE OF 20,000

Autoantibodies are typically associated with a structurally normal heart.

The most vulnerable period is from 16-24 weeks and it rarely develops after 30 weeks of pregnancy. The RO/LA antibodies causing fibrosis in the conductive system in the heart including the AV nodules.

Among all causes of congenital complete heart block, neonatal lupus is responsible in 90-95% of cases.

More than 90% of the mothers of affected offsprings have anti RO antibodies and 50-70% have anti LA antibodies (<1% in general population). CHB is found in 2% of mothers with antibodies.

Diagnosis:
Bradycardia and anti RO/LA with cardiac failure eventually causing hydrops (80% mortality).

Congenital heart block in first trimester with bradycardia, nuchal translucency and severe cardiac anomalies have extremely poor prognosis.

Management:
In case of suspected myocarditis: steroids and plasmapheresis may be successfully used but are without effect on the conductive system. Some suggest

Dexamethasone (cross placenta) from 24 weeks through the end of pregnancy. Incomplete heart block has been reversible on steroid therapy and has suppressed the associated pleuropericardial effusion and hydrops as well as antibodies, but the stsudy is based on limited data. Half of the patients who survived need pacemaker in later life. Neonatal mortality is high (20%). Often delivered by Cesarean section because of difficulties to interpret CTG and achieve optimal neonatal service. Pulse oximetry can be used during labour.

Recurrent Risk:
20% if one and 50% if two children are affected. There is Llimited data on the effects of glucocorticosteroids before 16 weeks of mothers with antibodies. But should be considered if next baby has a high risk bacause in one study no congenital heart block was found in 25 children treated before 16 weeks.
Cases of incomplete heart bloch has been reversed when dexamethason and betamethason has been given in the rest of pregnacy.

References:

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(2) www.uptodate.com 2007

NECROTIZING INFECTIONS OF THE SKIN AND FASCIA

INTRODUCTION

Necrotizing infections of the skin and fascia include necrotizing forms of cellulitis and fasciitis types I and II. These infections are characterized clinically by fulminant destruction of tissue, systemic signs of toxicity, and a high rate of mortality.

NECROTIZING CELLULITIS

There are several different types of necrotizing cellulitis including clostridial and nonclostridial anaerobic infections.

Clostridial cellulitis — Clostridial cellulitis, most often due to Clostridium perfringens, is usually preceded by local trauma or recent surgery. Gas is invariably found in the skin, but the fascia and deep muscle are spared. Magnetic resonance imaging (MRI) or CT scanning and measurement of the serum creatine kinase (CK) concentration can help to determine if muscle tissue is involved.

Nonclostridial anaerobic cellulitis — Is due to infection with mixed anaerobic and aerobic organisms that produce gas in tissues. Unlike clostridial cellulitis, this infection is usually associated with diabetes mellitus and often produces a foul odor. It must be distinguished from myonecrosis and necrotizing fasciitis by surgical exploration

NECROTIZING FASCIITIS

Necrotizing fasciitis is a deep seated infection of the subcutaneous tissue that results in progressive destruction of fascia and fat, but may spare the skin. Two clinical types exist.

- Type I necrotizing fasciitis is a mixed infection caused by aerobic and anaerobic bacteria and occurs most commonly after surgical procedures and in patients with diabetes and peripheral vascular disease.

- Type II the bacteria that causes these infections was originally identified as haemolytic group A streptococcus (GAS, Streptococcus pyogenes) and 50% have no obvious portal of entry, but subsequent observation have implicated nummerous other aerobic and anaerobic which often acts synergestical i.e Staphylococcus aureus (meticillin-resistent), clostridium perfreingens and sardellii . Almost one-half had streptococcal toxic shock syndrome.

In contrast to type I necrotizing fasciitis, type II can occur in any age group and among patients who do not have complicated medical illnesses.

Fournier's gangrene — In the perineal area, penetration of the gastrointestinal or urethral mucosa by enteric organisms can cause Fournier's gangrene, which is an aggressive infection. These infections begin abruptly with severe pain and may spread rapidly onto the anterior abdominal wall, and into the gluteal muscles. These infections

are induced by a mixture of aerobic and anaerobic organisms and are therefore classified as type I infections.

Clinical manifestations — Early recognition of necrotizing fasciitis is important since there may be a remarkably rapid progression from an inapparent process to one associated with extensive destruction of tissue, systemic toxicity and loss of limb or death.

Unexplained pain, which increases rapidly over time, may be the first manifestation of necrotizing fasciitis. Whenever postoperative/posttraumatic pain is increasing in severity, the patient should be examined expeditiously to verify that a serious wound complication, such as necrotizing fasciitis, is not the source of the increasing pain. Thus the triad of incordinate pelvic pain, oedema (unilateral) and any sign af septicemia in the post partum period create a high suspision on necrotizing fasciitis and mandate imediately surgical intervention.

Erythema may be present diffusely or locally. Within 24 to 48 hours, erythema may develop or darken to a reddish-purple color, frequently with associated blisters and bullae; bullae can also develop in normal appearing skin. Once the bullous stage is reached, there is already extensive deep soft tissue destruction such as necrotizing fasciitis or myonecrosis. Crepitus is present in about 10 percent of patients. GAS production does not play a significant role in the early diagnosis. GAS is seen by X-ray, CT-scan or magnetic Imagining (MR) and should be obtain if the diagnosis is in doubt.

Awaiting results of blood cultures or skin aspirates should not be done. Surgical exploration should proceed rapidly if this diagnosis is suspected. The patient can develop bakteriaemia –sepsis – sepsis shock and multiple organ dysfunction syndrome (MODS).

Recommendations:

- When necrotizing fasciitis is suspected, surgical exploration is the only way to be certain whether this is the correct diagnosis (fever, toxic symptoms , soft tissue involment and pain out of proportion with skin findings and elevated CRP with or without radiological findings.

- Aggressiv volumensubstitution

- Prompt surgical exploration both facilitates early debridement and obtaining material for appropriate cultures.

Clindamycin may be more effective because it is not affected by inoculum size or the stage of growth, it suppresses toxin production, it facilitates phagocytosis of S. pyogenes by inhibiting M-protein synthesis, it suppresses production of regulatory elements controlling cell wall synthesis and it has a long postantibiotic effect. Recently, a retrospective analysis of cases demonstrated a greater efficacy for clindamycin compared to beta-lactam antibiotics in patients with invasive infections.

Some recommend the administration of penicillin G (4 million units intravenously every four hours in adults >60 kg in weight and with normal renal function) in combination with clindamycin (600 to 900 mg intravenously every eight hours). RH in Denmark Menonem 2 g IV and then 1 g x 3 Cepoxin 400 mg x 2, Dalacin 600 mg x 3 and Gammaglobolin 25 g daily for 3 days.

Antibiotic therapy should be narrowed based upon operative culture results and susceptibility for at least 10 days

References:

(1) Nekrotiserende Fascit: Guidelines from Rigshospitalet, Copenhagen

(2) www.uptodate.com 2007

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)

Definition: Thrombocytopenia < 150 x 10^9/L in 0.9% of neonates. 1/3 will be immune thrombocytopenic. Severe thrombocytopenia (< 50 0,12-0,24%).
Feto-maternal incompatibility for platelet antigens inherited from the father but do not cause maternal thrombocytopenia.

Mother forms IgG class antiplatelet antibodies against the neonatal fetal platelets antigens inherited from the father. These antibodies cross the placenta and destroy fetal platelets resulting in fetal and neonatal thrombocytopenia. In contrat to RH immunisation NAIT often developes in first pregnancy.

- Anti HPA-1a previous Zwa 75-80%
- Anti HPA-5b previous Zwa 15%
- Anti HPA-15b previous Zwa 4%

Incidence: 1:1000 more than half in first pregnancy
Recurrence 75%-90% same or worse (Father can be heterozygote). Mother at increased risk if HLA-BB, DR 3 or DRW52.

Risk: If fetal platelets < 50 great risk of intracranial hemorrhage.
The most serious complication is intracerebral haemorrhage which occur in approximately 10-20% of affected newborns; one quarter to one half of these occur in utero.

Screening: Maternal antigen typing if a maternal sister had a pregnancy complicated by NAIT or a histsory suggestion of this diagnosis and demonstrate specific antibodies directed against the antigen.

Ultrasound before .
Vaginal delivery increased risk for cerebral hemorrhage.

Vaginal delivery contraindicated if fetus is affected. However some will argue that
vaginal delivery is possible if fetus has effective treatment.
Affected infant should have Cesarean section around 36 weeks.

Management:

Amniocentesis is prefered as CVS is associated with a theoretically increased risk of maternal sensitivity in case of affected fetus.

If suspicion of an affected infant, check the zygocity on both parents.
If husband is heterozygote, CVS/amniocentesis assess fetal DNA and determines infants antigen status (PCR).
If fetus HPA-1a negative – no risk

If fetus HPA-1a positive - great risk for thrombocytopenia
Cordocentesis on fetus at risk from 20-24 weeks and treat if necessary with platelets or possible steroids.

If HPA-negative mother delivers 15% of infants HPA negative.
Antenatal ultrasound can show cerebral bleeding, porencephaly and ventriculomegaly. Ultrasound is the standard technique. MRI research tool.

The most widly accepted strategy in United States is widly antinatal administration of gammaglobulin (IVIG) typically instituted at 20 weeks.
No consensus of optimal protocol for managing IVIG after it is began. Can be given with prednisone 1 mg/kg/week. Platelet transfusion used as the last resort.

Treatment Options: Management should be planned in a fetal medicine unit.

Cordocentesis on fetus at risk from 20-24 weeks. If previous affected siblings, the platelets is < 20,000/μL in 50 percent of fetuses.

The blood sampling should check success of treatment and several transfusion weekly can be necessary.

Neonatal:
Use HPA compatible donor platelets. When available mother platelets will not react and the maternity derived anti-platelets antibodies.

IVG and corticosteroid not well documented and controversial.

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(1) Berhowitz RL, Bussel JB, McFarland JG. Alloimmune thrombocytopenia: state of the art 2006. Am J Obstet Gynecol 2006 Oct;195(4):907-13. Epub 2006 Jul 26.

(2) Ghevaert C et al.Management and outcome of 200 cases of fetomaternal alloimmune thrombocytopenia. Transfusion2007;47(5):901-10.

(3) www.uptodate.com 2007

PARVOVIRUS

The fifth disease: Erythema Infectiosum (slapped cheek syndrome). 50-75% of women at reproductive age are immune.
Epidemics every 3-6 years. Seroconvertion 13% during epidemic and 1% if no epidemic.

Background: Infection affects the bone marrow and can cause anemia especially among fetus which can cause hydrops.

Diagnosis: Flue like symptoms followed 1-4 days rash (not at all get it) and 30% arthritis like joint involvement.
IgM 3 days after the symptoms and persist 3-4 months. IgG after 7 days. Incubation period 1-3 weeks. Infection before symptoms and probably not infection after onset of rash and arthritis like symptoms. IGM positive the diagnosis is confirmed. IgG only positive no infection the last 4-6 weeks. If IgG and IgM are both negative, repeat test within 2-3 weeks.
Infection in the fetus can be confermed by Parvovirus DNA.

Risk: No risk for malformation. The transmission rate is the risk for infection is 50% in families, teachers 20-30%. The risk of fetal death is largely confined to maternal infection within the first 20 weeks. Fetal death presented in the first 16 weeks are most often not accompanied by hydrops. The peak incidence of Parvo-virus associated hydrops-foetalis is between week 17 and 24.

Risk for fetal demise less than 3% and highest in second trimester. Risk up to 10 weeks after infection usually within 3-6 weeks. The risk for fetal hydrops is 2-4%. The risk for hydrops decrease after 20 weeks and is 2-4 % before 32 weeks and less than 1 % after 32 weeks. The risk of fetal death is very small after 20 weeks.

Fetal anemia causing ascitis and/or hydrops. Hydrops further caused by myocarditis, hypo-albuminemia (liver damage) and venous obstruction caused by placenta-edema and liver enlargement. Fetal Hgb in hydropics range from 2.1–9.6.
Spontaneous resolution occur in 30% but a rare events in severe hydrops.

Handling: Sero-negative women should not work in child institution when there is an epidemic but stay home until 6 weeks after the last child has had symptoms.

In case of infection. Ultrasound every second week until 10 weeks after infection to see if the child develops ascites/hydrops mean 6 weeks or until 30 weeks.

In severe cases, intrauterine infusion with survival 85% mild to moderate, hydrops disappear spontaneously in 50% of cases. Few cases describe in which anaplastic anemia has been observed in infants treated by intrauterine transfusion.

Intrauterine death is also seen without development of ascitis/hydrops. Therefor many advocated for parvovirus DNA analysis

No indication for termination.

References:

1) Crane J. Parvovirus B19 Infection in Pregnancy. SOGC Clinical Practice Guidelines No. 119. September 2002.

2) Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. Prenat Diagn 2004;24:513-18

3) www Infpreg.com

4) www.uptodate.com 2007

PRETERM PREMATURE RUPTURE OF MEMBRANES (PPROM) (< 34 [37] weeks)

Definition: Rupture of membranes prior to onset of uterine contractions before 37 weeks of gestation.

Prevalence: 1-2% and preceed about one third of preterm deliveries.
The risk of chorioamnionitis is higher during the first 5-7 days after rupture of membranes indicating that infection is likely etiology. After the 1st week chorioamnionitis is around 30%.

Diagnosis and Observation:

Cardiotocography
Sterile speculum examination: Fluid coming
from cervix (when coughing) or in posterior fornix, look for umbilical cord prolapse
Digital cervical examination should be avoided as it increase the risk for infection.
Amniotic fluid confirmed by Nitrazine paper
pH > 4, 5 or ferning
Test or diamine-oxidaze/fetal fibronectin
Vaginal swab

Chorioamnionitis:

Matenal pyrexia > 37,8 offensive vaginal discharge and fetal tachycardia > 160 beats/minut indicate clinical chorioamnionitis, fetal tachycardia predict 20-40% of cases with a false positive rate of about 3%.

Uterine tendernes:

Decrease fetal moments WBC and CRP increases indicate intraurine infection. Is found in 40% of cases but amniocentesis is not rcommended routinly.

Ultrasound: Measurement of amniotic fluid, urinanalysis and vaginal culture

Management: Conservative management if no signs of chorioamnionitis or obstetric indication for delivery

- Steroids 24-34 weeks: 12 mg Dexamethasone immediately and after 12 hours if not given before.
  Women wiwth PPROM and uterine activity should be considered for tucolysis if they require intrauterine transfer and antinatal corticosteroids.

- Prophylactic antibiotic. (In the Oracle health beneficial effect was only found for erythromycin). Longer duration than one week increase the risk for resistance.

  Erythromycin 500 mg x 3 p.o or (alternativ 1 g IV/IM the first 24 hours).
  Ampicillin 500 mg x 3 p.o.or (alternative IV/IM 1 g x 3 first 24 hours).
  The above antibiotics can be given together with Metronidazol 1 g x 4 i.v. then 500 mg p.o. every 6 hours for 1 week or suppositories 500 mg x 3.

If broader spectrum of coverage is needed or patient has allergy to Ampicillin: Ceftriazone 1 gm IV daily.

If β-hemolytic streptococci colonization or patient is a known carrier (see guidelines for GBS syndrome).
Antibiotics given for one week.

Cerclage: Be kept in situ for 24 hours to give time for antibiotics and steroids to work. Some will Keep cerclage to avoid manipulation of the cervix. Remove if any contractions.

If amnionitis: Start antibiotics 2 g Ampicillin IV every 6 hours and sup. Metronidazol 500 mg x 3. If patient is on these antibiotics change to another (resistent bacteria) (clindamycin 900 mg intravenously every 8 hours or Gentamycin 1,5 mg/kg i.v. every 8 hours)

Delivery in hours (induction or Cesarean section).

Prognosis: Gestational age < 20 weeks, up to 15% of the children will survive, with the risk of severe handicap of 50%.
If oligohydramnios the prognosis is very dubious.
20-24 weeks gestational age. Antibiotic if one wants to give the pregnancy a chance.

Steroids to be given 2 days before "active obstetrics" is indicated
Tocolysis normally not indicated, can sometime be used to get steroids to work.

Elective Induction:
From 34 weeks with antibiotics during

References:

(1) ACOG Practice Bulletin No. 80. Premature rupture of membranes: Obstet. Gyncol. 2007;109(4):1007-19

(2) Falk SJ et al. Expectant managemenet in spsontaneous preterm premature rupture of membranes bertween 14 and 24 weeks' gestation. J Perinatol. 2004 Oct;24(10):611-6

(3) Royal College of Obstetriciand and Gynecologist Guideline No. 44, Nov. 2006

(4) www.uptodate.com 2007

PREMATURE RUPTURE OF MEMBRANES (PROM) (>34 [37] WEEKS)

Prevalence: 8% of pregnancies at term.

Women will deliver < 24 hours 70%
< 48 hours 85%
< 72 hours 95%

Risk: Longer duration of rupture risk for
Amnionitis (6-10%)
Postpartum endometritis (3%) – (10-30% after C/S
Neonatal infection (1-3%)
70% will deliver in less than 24 hours
85% will deliver in less than 48 hours

Diagnosis: See PPROM

Some obstetricians go for prompt induction with oxytocin because of small reduction in maternal and neonatal infection rate. Other prefere short term expectation < 24 hours.

Management:
Either acute induction (prostaglandin in case of unripe cervix).

Conservative Management:
(short term expectant: < 24 hours. [In some studies decreased Cesarean section rate].
Temperature measured twice daily.

Antibiotic or if not in after 18-24 hours. If GBS positive, see GBS syndrome.
Gestational weeks 34 + 0 – 35 + 6 can be treated as PPROM.

Induction of :
Comparing the use of oxytocin to PGE2 (vaginal or intracervical) in women with ruptured membranes, the use of prostaglandins resulted in some studies higher success and satisfaction rate.

Oxytocin is preferable in case of a ripe cervix as neonatal infection rate and endometritis seems to be decreased compared to Prostaglandins.

References:

(1) Dare MR et al. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes aat term (37 weeks or more). Cochrane Database Syst Rev. 2006 Jan;(1):CD005302.

(2) Dare MR. Premature rupture of membranes. ACOG Practice Bulletine No 80. Obstet Gynecol 2007;109:955-55

(3) Royal College of Obstetriciand and Gynecologist Guideline No. 44, Nov. 2006

(4) www.uptodate.com 2007

PRETERM WITH INTACT MEMBRANES

Definition: before 37 weeks of gestation < 259 days and > 20 weeks.
Occurs approximately in 5-10% of pregnancies.
Extremely preterm before 28 weeks of gestation (1%).

Prognosis: Regular persistent uterine contraction (lasting 30 seconds or longer) and with a maximum of 5 minutes interval in 20 minutes with progression in cervical effacement and/or dilatation.

Treatment: If no contraindication, tocolysis is indicated to postpone for up to 48 hours to get optimal effect of steroid Betamethasone 2 doses of 12 mg /ml 24 hours apart from 23-0 weeks up to 32 or 34 completed weeks.

Initial Evaluation: History and physical examination including specular sterile vaginal examination and cervical ultrasound if needed with documented cervical status. Further digital examination should be avoided unless patient is in active .

Cardiotocography
Ultrasound

- Fetal presentation and number
- Placenta localization
- Fetal weight and abnormalities survey if not performed previously
- Biophysical profile especially amniotic fluid index and fetal breathing. Fetal breathing less likely to occur if the women are in true labor.
- Cervical assessment by ultrasound $\geq$ 2,5 (1,5) cm unlikely to be in case of premature .
- Fibronectin useful as negative predictive value is high.

Urinanalysis and culture
Vaginal culture (inside introitus)
Serum electrolytes, creatinine and glucose, glucosuria and ketonuria

Antibiotics:
Although a prolongation in time to delivery and a trend towards a reduction in neonatal sepsis antibiotics cannot be recommended with intact membranes because of raised concerns about increase perinatal mortality for those who received antibiotics.

Contraindication to Tocolysis:
Abnormal vaginal bleeding – abruption
Severe hypertension
Chorioamnionitis
Fetal distress
Fetal abnormality and demise

TOCOLYSIS
Acute

Acute tocolysis: Glycerolnitrate (Nitroglycerin) or Terbutaline.
Myometrial relaxation within seconds after Nitroglycerin and the duration is 2-3 min.

Indication:
(1) Fetal distress caused by hypercontractility or before section if fetal heart rate is abnormal on contraction.
(2) Caesarean section if difficulties are anticipated such as transverse lie (Spray Sublingual at skin incision).
(3) Difficult delivery of the head in breech.
(4) Inversion of the uterus
(5) Internal version after twin A or difficulties during Cesarean section.
(6) Shoulder dystocia if Zavanelli maneuver is applied.

Dose:
Sublingual Nitroglycerin 0.25 mg or
Sublingual spray 0.4 mg/dose in case of anesthesia (can be repeated 2 times).
Alternative to Nitroglycerin is Terbutaline 0.25 mg IV.

Tocolysis in premature

There is still no clear evidence that tocolytic drugs improve outcome following but should be considered to gain a few days from course of steroids or in-utero transfer. If a tocolytic agent is used, Ritodrine no longer seems the best choice.
Alternative such as Atosiban or Nifedipine appears to have comparable effectiveness in terms of delivery for up to seven days and are associated with fewer maternal adverse effects and less risk of rare serious adverse effect. Nifedepine is not licensed as a tocolytic agent. Indomethacin, calcium channel blockers (Nifedepine) and Atosiban (Tractocile) should be considered first line according to British guidelines.
B-mimetics (Ritodrine and Terbutaline) has many side effects and therefore is not so often used nowadays.
Magnesium Sulfate: the effect is like placebo.

Multiple tocolytic agents have been suggested by some in very early gestation.

Atosiban Guidelines
Atosiban (Tractocile):
Selective oxytocin antagonist small placental transfer seems to be as effective as B-mimetic but questionable before 26 weeks and in twins. The side effects and diabetogenic is lesser than B-mimetics and should be used in case of severe adverse effects of B-mimetics and in case of gestational diabetes and hyperthyroidism.

***Side Effect - seldom**:*
Headache, nausea, vomiting, increase temperature, palpitation, hypotension, hyperglycemia, seldom itching, rash and sleeping disturbances.

Observation:
Blood pressure, ketonuria, and hourly the first 3 hours and after each micturition thereafter.

Procedure:

Stage	Procedure	Rate	Doses
1	Bolus 0,9 ml (7,5 mg/ml)	Within 1 minute	6,75 mg
2	Saturation-infusion (0,75 mg/ml)	24 ml/hour in 3 hours	18 mg/hour
3	Maintenance-infusion (0,75 mg/ml)	8 ml/hour for up to 8 hours	6 mg/hour

Bolus-injection: 0,9 ml Tractocile ampoule (7,5 mg/ml).
Saturation- and maintenance infusion: 100 ml NaCl. Remove 10 ml and replace with 2 ampoules of 5 ml Tractocile (7,5 mg/ml).

Calcium Channel Blockers:
Inhibits smooth muscle contraction by impeding the flow of calcium across the muscle cell membrane and reduce uterine vascular resistance.

Administration:
10 mg oral (Sublingual can cause acute hypotension) Nifedipine (Adelat) every 15 min until effect or max 1 time some start with loading dose of 30 mg followed by 20 mg po q 4 hour depending of uterine activity. Maintenance 10 mg q 8 hours up to 48 hours).
Slow release Nifedipine 60-160 mg/day.
Halflive 2-3 hours and action up to 6 hours.

Contraindication: Nifedipine and magnesium together can cause hypotension and affect the heart.
Cardiac disease. Heart failure (risk for AMI and severe hypotension) and severe liver disease.

Side Effect: Headache, blushing, nausea, dizziness, cranial Hypertension, hypotension and tachycardia.

Observation: Blood pressure: Pulse and ketonuria at start. Blood pressure and pulse every ½ hours, the first 3 hours. Ketonuria every 3-4 hours (after micturition).

Indomethacin
Seems to be as effective as B-mimetic
Up to 100 mg suppositories followed after 8 hours by 25 mg supp every 8 hours for max of 48 hours. If longer, echocardiography evaluation should be performed with signs of tricuspidal evaluation

Fetal side effects
Possible only after longer than 2 days treatment
Ductus constriction, tricuspid regurgitations, pulmonary hypertension and persistent fetal circulation.
Oligohydramnios, renal improvement

Recent metanalysis demonstrated an increased risk of perrventricular leucomalacia and necroting interocolittis.

Specific contraindications:

Cardiac disease, gastrointestinal bleeding, hepatitis, Diabetes, impaired renal function and oligohydramnios.

Not recommended more than 24 hours after 32 weeks (increased cardiac sensitivity).

B-mimetics seldom used because of sideeffects and atosiban and nifidepine appear preferable as they have or fewer adverse effects and seem to have comparable effectivenes.

Magnesium sulfate:

The litterature does not support on effect.

Rules of Thumb for the Prognosis in Preterm Infants (Sandbjerg)

Gestational age	24	25	26	27	28	29	32
Survival	40%	50%	60 %	70%	80%	90 %	>97 %
Normal among survivors	40%	50%	60 %	70%	80%	90 %	>97 %
Celeston & surfactant	The prognose 1-2 weeks better than gestational age						
< 85% of median weight	The prognose 1 week worser than gestational age						
< 75% of median weight	The prognose 2 weeks worser than gestational age						

From 23-24 weeks survival increase 3% for each day (Finnstroem 1999)

References:

(1) King J, Flenady V. Antibiotics for preterm with intact membranes. Cochrane Database of Systematic Reviews. Issue 2, 2002.

(2) King JF, Flenady VJ, Papatsonis DNM, Dekker Ga, Carbonne B. Calcium channel blockers for inhibiting preterm . Cochrane Database Syst Rev 2002(3).

(3) Tocolytic drugs for women in preterm . Royal College of Obstetricians and Gynecologists. Clinical Guideline No. 1(B). October 2002.

(4) Simhan HN, Caritis SN. Prevention of Pretence Delivery NEJM 2007;357:477-87

(5) www.uptodate 2007

RED GROUP CELL IMMUNIZATION (Rhesus Immunization)

The most frequent is: Immunization to the Rhesus (D) Antigen i.e.: when the Rhesus (D) negative mother becomes sensitized to Rhesus (D) positive red cells either by feto-maternal hemorrhage or previous transfusion. Only IgG-type and not IgM-type antibodies may cross the placenta and cause erythroblastosis of the fetus and hemolytic disease in the newborn (HDN).

The Rhesus antigen recognized on the red cell membrane includes D, C, c, E, e (there is no "d" antigen).

Causes:

(1) Failure of administration of anti-D prophylaxis
300 mcg (or 1500 IU) that neutralize 30 ml Rh-positive fetal blood, equivalent to 15 ml of fetal red blood cells ~ 99,2-99,3 of women have fetomaternal haemorhage less than 4 ml and 0,3% > 15 ml.

(2) Antenatal sensitization: The risk is 1-2% at the time of delivery in primaparas not treated in pregnancy before delivery while a total 8% will be immunized by 6 months postpartum.. Overall, approximately 16% of Rhesus D negative women become allo-immunized after two deliveries of Rhesus D positive ABO compatible infants. These risks can be reduced to 1-2% if a single dose of immunoglobulin is given after delivery and can be further reduced to 0.1% with addition of routine antenatal administration in the third trimester.

(3) Several red cells antigens can cause sensitization and erythroblastosis especially anti-K, anti-E, and anti-c (see table) with a prevalence of 0.3 in Rhesus positive woman.

Screening:

All pregnant women should be "typed and screened", the blood group determined, tested for Rhesus type and have an antibody screen (indirect Coombs' Test).
Fetal rhesus determinated if the paternal pheno type is heterozygotic amniocentese for determination of fetal blood type (CPCR).

Prophylaxis:

Rhesus immunoglobulin (Rhogam) should be given to all Rhesus negative mothers in case there are no antibodies and the infant is Rhesus positive or the type is unknown in the following situations:

(1) After delivery: Cord blood for type and direct Coombs' Test. 300 μg or 1500 IU anti D = Rhogam within 72 hours after delivery. If this time exceeded, Rhogam should still be given as it seems effective even up to 14 days.

If delivery occurs less than 3 weeks from the administration of Rhogam (see below) repeat dose is not required at delivery unless a large fetal hemorrhage is detected.

The half life of immunoglobulin is approximately 24 days, therefore 15-20% of women who is receiving immunoglobulin of 28 weeks would have a very low titer ($\leq$ 1:4) at term.

(2) Before 12 weeks of gestation some centers give, 50 μg (250 units), in case of abortion, CVS, ectopic pregnancy.

(3) After 12 weeks 300 μg (1500 units) in case of abortions, utero-invasive procedures (like amniocentesis, CVS, blood sampling, and fetal bladder drainage), external cephalic version, abdominal trauma in case of suspicion of extent feto maternal bleeding perform, Kleihaur test to quantify the volume of fetal hemorrhage. - 10 μg Rhogam neutralize 1 ml fetal blood.

Antibody Screen Positive Patients:
Antibody titer in saline is a measurement of IgM and albumin titer reflects IgM and IgG.

(1) If antibody to an RBC antigen known to cause isoimmunization is identified on the Indirect Coombs' screening test, an antibody titer is determined. The father of the pregnancy should be tested for the relevant red cell antigen and if positive, tested to determine if he is homo- hetero-zygous for the antigen. If the heterozygous/ homozygous the fetal blood group can be detected by amniocentesis, CVS or cordocentesis.

(2) If the Coombs' titer of an Rh antibody (or other antibody) is less than 1:16 (and this the FIRST pregnancy in which a positive titer is identified) and remains so on checks every 2-4 weeks, the patient can safely be allowed to continue the pregnancy until term when induction of may be indicated.

(3) If the titer is > 1:16 (Anti-Kell > 1:8) or if this is a subsequent (second, third, etc.) pregnancy where a positive Rh titer is noted, a more aggressive management (percutaneous umbilical blood sampling (PUBS), amniotic fluid analysis) is recommended, with intensive perinatal care throughout the pregnancy, /delivery and the neonatal period.

(4) A mother who has had a previous stillborn or hydropic infant due to Rh-isoimmunization has approximately a 90% risk of losing the next Rh positive fetus unless she receives meticulous prenatal care, regardless of the antibody titer.

Noninvasive Fetal Testing: Every 3-4 weeks

Cardiotocography (CTG) --
Sinusoidal pattern, a sign of severe anemia

Serial sonography:

- Polyhydramnios
- An increase in the size of the liver and the spleen are good predictors of anemia.
- Measurement of peak velocity of systolic blood Doppler flow in the fetal middle cerebral artery has a sensitivity of 100% and a false positive rate 12% for the detection of moderate or severe anemia. Values below 50 percentile seems to rule out anemia.
- Hydrops is a late sign of erythroblastosis.

Invasive Fetal Testing:

For fetuses at high risk of severe anemia, amniocentesis should be performed between 16-20 weeks to detect blood cell type (DNA analysis) and amniotic fluid bilirubin levels quantified by measuring the optical density by spectrometric examination. If positive, the result should be plotted in the modified Liley graph. Has been replaced by monitoring of MCA Doppler in many departments.

Zone I:

Reassuring although neonatal exchange transfusion maybe necessary, repeat amnio every 3-4 weeks. Patient with results in Zone 1 can be allowed to proceed to term.

Zone II:

Fetus may be affected, repeat amnio every 1-3 weeks. Declining values are encouraging although they do not exclude mild hemolytic disease. Stable or rising ΔOD measurements are a cause for concern, fetal blood sampling is indicated.

In case of declining results in the low mid zone patient can be allowed to go to 38-39 weeks.

Zone III:

Suggests severe hemolytic disease with high probability of fetal death within 7-20 days. Fetal blood sampling and transfusion is indicated.

Care should be taken to shield the amniotic fluid from light since this will falsely lower the delta OD 450. Decreases in the amniotic fluid optical density may also result from maternal corticosteroid administration.

Minor Red Blood Cell Antibodies Associated with Hemolytic Disease of the Newborn[1]

Blood System	Specific Antigens	Severity of hemolytic diseases of the newborn (HDN)
Kell	K	Mild to severe
	K	Mild
	K	Mild
	Kp(a)	Mild
	Kp(b)	Mild
	Js(a)	Mild
	Js(b)	Mild
Duffy	Fy(a)	Mild to severe
	Fy(3)	Mild
Kidd	Jk(a)	Mild to severe
	Jk(b)	Mild to severe
	Jk(3)	Mild
Lewis	Y	Not a cause of HDN
	Fy(b)	Not a cause of HDN
	P1	Not a cause of HDN
MNSs	M	Mild to severe
	N	Mild
	S	Mild to severe
	S	Mild to severe
	U	Mild to severe
	Mi(a)	Moderate
	Mf(a)	Moderate
	Vw	Mild
	Mur	Mild
	Hil	Mild
	Hut	Mild
Lutheran	Lut(a)	Mild
	Lut(b)	Mild
Diego	Di(a)	Mild to severe
	Di(b)	Mild to severe
Xg	Xg(a)	Mild
P	PP1(k)	Mild to severe
	P1	Not a cause of HDN

[1]Adapted from Weinstein, L. Clin Obstet Gynecol 1982;25:327 and Reid, ME, Toy, PTCY. in Hematology and Infancy and Children, 5th ed. Nathan, DG, Drkin, SH (Eds)m WBH Saunders, Philadelphia, 1998, p. 1768.

Reference:

(1) Cranethr C, Cochrane. Anti-D adminstrated after childbirth Royal College of Obstericians and Gynecologist. Use of anti-D immuniglobolin for RH prophylas (22) revvised May 2002

(2) David W. Cohen, MA, MT (ASCP) SBB. Hemolytic disease of the newborn: RBC alloantibodies in pregnancy and associated serologic issues.

(3) www.uptodate.com 2007

RUBELLA

Diagnose: IgG antibody increases after 1 to 2 weeks and/or IgM antibodies demonstrated. IgM antibodies disappear 4-8 weeks after the acute phase.

Examination: Exposition for rubella before 18 weeks of gestation. Rash in mothers with serological verified rubella (look for Parvovirus as well)

Incubation time: 14-21 days

Interpretation: No antibodies = never have had rubella. Repeat after 2 weeks if suspicion of recent exposure. Diagnosis should not be made on IgM antibodies alone. Disappear after 4-8 weeks. Increase in IgG and IgM antibodies equal to actual rubella infection. In very few occasion IgG develops before IgM. 80-90% of mothers in first trimester transfere rubella to the foetus and 50% in the second trimester.

Risk: 0-12 weeks of gestation, severe malformation (cataract, deafness, heart malformation, mental retardation) 50-85%. 13-16 weeks of gestation, hearing loss and/or mental retardation. 16-18 weeks of gestation, only hearing loss in few %. More than 18 weeks of gestation, no malformation described but child can excrete virus several years after delivery.

Fetal Diagnosis: Should be based on risk assessment as the necessary virological technique for fetal investigating is not fully validated. However, CVS with PCR seems to be better than amniocentesis and fetal blood sampling.

Postnatal Diagnosis:
0-3 months IgM indicates intrauterine infection.

Prophylaxis: Pregnancy is not advised 1 months after vaccination but damage has not been described even after accidental vaccination in the first trimester. No risk post partum and breastfeeding no contraindication.

References*:*

(1) MacLean A, et al. Infection and Pregnancy, RCOG Press 2001.

(2) www.Infpreg.com

(3) www.uptodate .com 2007

SHOULDER DYSTOCIA

Suspect in case of big infant especially diabetic and obese mothers.

The risk for reaching critical and potentially inreversiable status after 6-8 minuts.

To remember

H - Call for Help
E - Episiotomy
L - Legs (McRobert)
P - Suprapubic Pressure
E - Extend post-arm
R - Rotate post shoulder

McRobert maneuver and suprapubic pressure: Dorsal position, the knees adducted against the breast use fundal pressure or suprapubic pressure behind (Mazzanti) or pressure from one side to other (Rubin) with gentle downward pressure on the head.

If no success, perform episiotomy to get place for your hand.

Reverse Lovset (Wood Screw): Do not use fundal pressure and do not let the patient push. Put the hand behind the symphysis on the dorsal side of the child and press on the scapula to an oblique position or rotate 180o use eventually the other hand and press under the clavicular of the posterior shoulder in the opposite direction.

If no success, deliver the posterior arm by taking your hand in the vagina posterior in front of the baby. Take the hand or under arm and let it pass over the baby's chest whereby the shoulder and arm is delivered. Humerus normally fracture. Rotate the delivered posterior shoulder anteriorly (rotating in the direction of the baby's back so as to keep the delivered arm in front of baby's chest). This should enable delivery of the other arm which was originally anterior.
Knee – hand position. The mother is turnover and the posterior shoulder which is now the upper is attempted to be delivered. Has been advocated by some. I don't think it works if the above procedures has failed.

Symphysiotomy: Effective but seldom used because of fear for maternal morbidity.

Fracturing of the claviculae normally the anterior by pressure of the thumb.

If no success, give tocolysis (Terbutaline 0.25 mg) or Nitroglycerin spray 0.4 mg Sublingual IV replaced caput in

flex position push it up and then Cesarean section
(Zavanelli maneuver)

References:

(1) Bruner, JP, et al. All-fours maneuver for reducing shoulder dystocia during . J Reprod Med 1998; (48):439-443.

(2) Dildy GA. Shoulder dystocia: risk identification. Clin Obstet Gynecol. 2000 June;43(2):265-82. Review.

(3) Gurewitsch ED. Optimicing shoulder dystocia management to prevent births injury. Clini Obstetric Gynecol 2007 Sep;50:592-606.

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SKIN AND PREGNANCY

1. Physiological skin changes related to pregnancy
2. Dermatoses modified by pregnancy
3. Dermatoses caused by pregnancy

Physiological skin changes related to pregnancy

Increased pigmentation especially in dark-haired women
Increased size and number of melanocytic nevi
Chloasma i.e. irregular hyperpigmentation in forehead and temples of face. *Use sun blockers and hydroquinol crème, 2 or 4%, for bleaching*
Increased hair growth with ensuing postpartum hair loss
Mild hirsutism
Increased sebum production with acne
Topical treatment like adapalene gel, or benzoyl peroxide 5 – 10% cream
Brittle nails
Increased tendency of sweating with miliaria rubra on trunk
Topical low-potency steroids and/or calamine lotion
Small hemangiomas, vascular spiders
Laser treatment or electro-coagulation
Varicose veins of legs and risk of haemorrhoids
Compressive stockings
Edema of face, hands and feet – most pronounced in the morning
Gingivial oedema and redness (in up to 80% of pregnant women): *Prevented by good oral hygiene*

Dermatoses modified by pregnancy

Increase of skin infections because of reduction in cell-mediated immunity
Candidiasis: clotrimazole or miconazole in a cream bases
Trichomoniasis: metronidazol
Condyloma acuminata never treat with podofyllin; physical removal
Herpes simplex: topical or systemic treatment
Pityrosporum folliculitis on trunk ketoconazole shampoo
Scabies permethrin cream
Dermatophytosis: – treat with topical therapy only - econozale, ketoconazole, lamisil

Atopic eczema has a variable course during pregnancy, but the mother often fights eczema of the nipples during breast-feeding and irritant hand eczema postpartum due to increased skin irritation.

Topical steroid therapy during pregnancy for eczema, psoriasis or other diseases does not give any risks for the child even though small amounts of the steroids are absorbed. Tacrolimus and pimecrolimus (topical calcineurin-inhibitors used for treatment of atopic eczema) should not be used as no experience exists. However, they are not absorbed and will likely not influence the pregnancy.

Dermatoses caused by pregnancy

Itching – or pruritus – affects up to 1/5 of pregnant women. An underlying skin disease should be considered including eczema, urticaria, psoriasis, scabies, drug eruptions. Therapy will be according to an eventual diagnosis.
Anti-histamines can be tried and do not increase the risk for the child. They are of course most effective for urticarial pruritus.

Intrahepatic cholestadid of pregnancy (Pruritus gravidarum) (also called obstetric cholestasis)
Between 0.02-2.4% of pregnancies develop itching in the third trimester beginning on the abdomen, but can become widespread. There are no evident cutaneous changes. Liver enzymes often slightly elevated and the patients can be mildly icteric. In one study on 693 women no complication were seen with bile acid level < 40 micromol/L. The pathophysiology is considered to be a mind cholestasis. If present, during several pregnancies it is associated with increased risks of cholelithiasis.

Obstetric cholestasis (Pruritus gravidarum)

Incidence: The incidence is higher in Scandinavia, Chile and China, family history in 35 %.
Starts in the second half of pregnancy usually in the third trimester.

Diagnosis: Pruritus without rash, worse at palms of hands and soles of feet.
Mild elevated transaminase < 3 fold very seldom up to 10 fold.
Alkaline phosphatates slight increase.
Raised gamma-glutamyl transpeptidase (yGT) (about 20 % of cases)
Bilirubin mild elevation (less common)
Increased (10 to 100 folds) serum bile acid (but normally nok available).

Differential Diagnosis:
Hepatitis, primary biliary cirrhosis, sclerosing cholangitis, gall stones.
Eventually rule out by liver ultrasound, viral serology (for hepatitis A, B and C, EBV, CMV)
Liver autoantibodies (for pre-existing liver disease, anti-smooth muscle antibody/chronic active hepatitis, antimitochondrial antibodies/primary/ biliary cirrhosis).

Maternal Risk: Postpartum bleeding caused by Vitamin K deficiency

Fetal Risk: Stillbirth, risk increases towards term, but does not correlate with maternal symptoms or transaminase levels. Preterm and fetal distress, intracranial.

Management: Mother counseled concerning possible risk to the fetus and the need for closer surveillance (fetall movements, fetal growth, CTG, liquor volume Doppler), but fetal death seems to be sudden.
Regular liver function test including Prothrombin time.
Early delivery at 37-38 weeks but in over 1.500 active managed pregnancies 13 of 18 stillbirth happens before 37 weeks. In sever cases such as jaundice delivery should be considered at 36 weeks..
Vitamin K 10 mg orally from 32 weeks to reduce the risk of fetal and maternal bleeding, K vitamin to the infant.

Treatment: Antihistamine may provide some sedation at wight but no significantly have an impact on pruntus.
Topical options: Diprobase ®, Balnium ®, Calamine lotion, cream with mental may provide some relief.
Ursodeoxycholic acid (UDCA) (Cholorectiv agent) reduce serum bile avcids 1,000 to 1,500 mg daily in 2-3 divided doses.

Dexamethasone 12 mg orally daily (few studies).
S-adenosylmethionine intravenously (few studies) (not recommended by RCOG).

Herpes gestationis (or pemphigoid gestationis)
Is rare affecting 1 : 150 000 pregnancies, but well-known because of very severe itching, urticarial or vesiculo-bullous skin lesions
(resembling herpes) and linear band of IgG at the basal membrane in the skin – like bullous pemphigoid. It normally starts in the second trimester and will resolve postpartum although this may
take several weeks. Topical potent steroid cream combined with antihistamines is the treatment of choice, but may be insufficient so a low dose of systemic steroid is necessary.

Pruritic urticarial papules and plagues of pregnancy (PUPPP)
This condition is by some regarding as three different diseases (polymorphic eruption of pregnancy, prurigo of pregnancy and pruritic follculitis of pregnancy).
However, they do have overlapping clinical symptoms and can for therapeutical reasons be lumped. What is important is that immnofluorescence investigation of a skin biopsy is negative. The condition is common, 1 in 240 pregnancies. The itching starts in third trimester and often in primigravidae, but it can start in the second, too.
Clinically there are urticaria, papules and eventually plagues. In some patients a more follicular pattern is prominent. Initial symptoms are on the abdomen, but they can spread to the extremities.
Topical steroids and anti-histamines should be tried first. The condition may be related to abnormal weight gains and claimed that the excessive weight gain stretches the abdominal skin leading to the irritation.

Striae distensae
This is a common phenomenon. There is no good prophylaxis, but routine usage of emollients with a gentle massage of the skin may delay and diminish their development. There is no cure although the use of excimer laser is claimed to promote fibroblast activity. Well-conducted studies are lacking.

References:

(1) Nielsen Piercy C. Handbook of Obstetric Medicine 2002. Martin Daniel Ltd

(2) Obstetric Cholestasis. Royal College of Obstrecians and Gynecologists Guideline 43. January 2006

(3) Rook, Wickensson, Ebling. Textbook of Dermatology Ed. 1998. Blackwell.

STREPTOCOCCAL TOXIC SHOCK SYNDROME (TSS)

Group A streptococcus **(GAS)** or Streptococcus pyogenes

Are facultative anaerobic gram positive cocci most known to cause pharyngitis. They can cause infection in the skin, vagina and soft tissue causing necrotizing fasciitis and myositis. They are B-hemolytic and produce toxin that may cause STSS, scarlet fever, rheumatic fever and glomerulonephritis.

One % of women in the reproductive age are colonized with GAS in the vagina.

Streptococcal Toxic Shock Syndrom is described in two clinically very different ways (1,2). The diagnosis is made according to the definition.

Isolation of GAS from a normal sterile body site, hypotension with systolic blood pressure ≤ 90mm at lest after 4 hours renal impairment.

Soft tissue infection that usually progress to necrotising facitis or myocitis.

Coagulopathi eg. (Throbocythophenia, DIC), liver involvement.

Adult respiratory distress symdrom.

Erythromacular rash and multiple organ failure. The mortality rate is 30. It can also develop hours to days after delivery. The patient has often a low platelet count and may initially present with leucophinia before rising the leucocyt count.

The perinatal group experience a rapid course before, under or immediately after delivery. In 50% the delivery is preterm. Half of the women present with very frequent and painful labour mimicking abruption of the placenta. The fetal mortality is high (59%) and the maternel mortality is very high > 50%. Retrospectively in 50% of cases a member of the family had had a sore throat.

The puerperal group develops 12 hours to several days after delivery. The delivery is usually at term. The fetal mortality is 0 but the maternal mortality is high. Symptoms are often diffuse in the stomach (may mimic peritonitis and pelvic inflammatory disease) or localized to an extremity. The latter pains are abrupt in onset. Influenza-like syndrome, fever but hypothermia may be present in patients with shock. The patient normally becomes hypotensive within hours. They have renal dysfunction with a rise in creatinin. They often have low platelet count and initially present with leucopenia, before a rise in leucocyt count. Necrotizing fasciitis is seen in approximately 50% with STSS of puerperal type.

Complications:

Acute respiratory distress syndrome (ARDS)

Occurs in half of the patients. Scarlatina like erythema may occur (10%).

Virulence factors:

The bacteria produce exotoxins ABC (SpeA,SpeB,SpeC) structurally very similar to Toxic shock syndrome toxin 1 produced by staphyloccus aureus.

The toxins function as superantigens causing the immune defence of the body to overreact to the infection. This leads to multiorgan failure and mortality is high (4).

Differential Diagnosis

Staphylococcal toxic shock syndrome (often no bacteriaemia and no localized pain). Gram negative sepsis (uncommon in healthy females) and typhoid fever. Acute meningococcemia, Rocky Mountain spotted fever.

Diagnosis :

Culture, blood, urin, cervix, wounds, nose and pharynx.

Treatment:

1. Surgery. Prompt and aggressive exploration and debridement.
2. Antibiotics. Duration individualized but if bacteremic usually continue for 14 days.
   Penicillin 4 mill IEx6 or 5 mill IE every 9 hours and Clindamycin 900 mgx3 (allergy: erythromycin instead of penicillin). Penicillins are more rapidly bactericidal versus Staphylococcus aureus than is clindamycin. However, Clindamycin is not affected by inoculums size or stage of growth. Suppress the synthesis of bacterial toxins, suppress synthesis of penicillin bindig proteins and suppress tumor necrosis factor.
3. Immunoglobulin (IVIG) 1 g/kg/day day one followed by 0,5 g/kg/day day two and three.
4. Treatment with pressor substance often norepinephrine and dopamine.
5. Massive intravenous fluid 10-20 L are often necessary to maintain perfusion.
6. Asymptomatic carrieres should have Penicilin for 10 days.
   Ref.: se under Staphylococcal toxic syndrome.
7. Experimental: Hyperbar oxygen treatment has been used in case of necroting facitis and myositis TNF antibodies has not been evaluaed in clinical studies but promising results in animal models.

STAPHYLOCOCCAL TOXIC SHOCK SYNDROME (TAMPON SYNDROME)

Staphylococcal aureus producing exotoxins causes diseases because they are superanatigens activating T-cells resulting in massive cytotoxin production (interleukins tumor necrosis factor and interferon). Toxic shock syndrome toxin (Superantigens) –1 (TSST-1) and other enterotoxins (A, C, D, E and H) Methecilin resistents staphylococcal aureus can cause the syndrome.

Symptoms:
Temperature > 38,9oC, hypotension < 90 mmHg
Multisystem involment: 3 or more of the following.
Gastric intestinal: vomiting and diarrhea.
Muscular: Severe myoalgia CPK > 2 times normal upper limit.
Mucous membranes hyperemia.
Renal: Se-creatinin > 2 times upper limit or pyuria
Hepatic: Bilirubin transaminase > 2 times normal upper limit.
Hemathologic: Platlets < 100.000 µ/L
CNS system: Deterioration.
All patients have fever, hypotension and skin manifestation (macular erythema) with a mean of 2 days after surgery with desquamation 1-2 weeks after onset of illness, particularly involment palms and soles.

Differential diagnose:
Streptococcal TTS (severe pain), meningococcemia (petechia) and Rocky Mountain spotting fever.

Treatment:
- Extensive fluid replacement for many days (10-20 liters/day)
- Remove tampons
- Drainage of any identified focus
- Clindamycin (600 - 900 mg i.v) q 8 hours plus Oxacillin or Vancomycin 30 mg/kg/day in two divided doses, Nafcillin 2 g IV q 4h/
- Intravenous Immunoglobulin (IVIG) 400 mg/kg over several hours
- Corticosteroid. Methyl prednisoline 10-30 mg/days
- Immune modulatory agents? re: Pentoxylline

Reference:

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3) Udagawa H, Oshio Y, Shimuzu Y. Serious group A streptococcal infection around delivery. Obstet Gynecol 1999;94:153-7.

4) www.Infpreg.com

5) **www.**uptodate**.com** 2007

THROMBOCYTOPENIA IN PREGNANCY

- Spurious
- Benign gestational (see below)
- Neonatal alloimmune thrombocytopenia (see page 70)
- Autoimmune (idiopathic thrombocytopenic purpura (ITP))
- Drug related
- Systemic lupus erythematosos (SLE, see page 63) and antiphospholipid syndrome (APS, see page 5)
- HELLP syndrome (see page 43)
- Disseminated intravascular coagulation (DIC)
- Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (HUS/TTP) (see page 44)
- Bone-marrow suppression
- Folate deficiency
- Hypersplenism

Gestational thrombocytopenia
Up to 8% of pregnancies, typical >70,000 and two-thirds 130.000-150.000 asymptomatic, normalized after 8-12 weeks after delivery.
Some suggest mild form for ITP (se below)
No definite diagnostic tests distinguished from mild ITP,
the mother should be monitored closely and epidural considered if platelets is above 50,000-80.000.

ITP - Idiopathic (autoimmune) Thrombocytopenic (purpura)
- Autoantibodies of IgG types. Measurements of antibodies are useless.
- Often known before pregnancy with history of treatment with autoimmune disease treated with steroids, gamma globulin and splenectomy. Fetal neonatal asymptomatic thrombocytopenica in 10-30% of cases, lowest day 2-4.
- Very little risk for serous fetal thrombocytopenica but splenectomy and platelets < 50.000 during pregnancy in mothers increase the risks. Cord blood not indicated.
- Cesarean section only on obstetrics indications.

Management

Platelets > 50
Control every 2-4 weeks
No epidural if < 80

Platelets < 50
Medical treatment with Prenisone 1-2 mg/kilo.
Response after 3-7 days
max. within 2-3 weeks.
Intravenous immune Globulin (IVIG) response after 72 hours.
Return to pre-treatment levels after 30 days.
If < 20 thrombocytes, transfusion first (6-10 U).
Splenectomy if failed steroid and immuno-globulin and platelets < 10.000

References:

(1) ACOG Practice Bulletin Number 6, September 1999.

(2) Burrows RF. Platelet disorders in pregnancy. Current Opinion in Obstetrics and Gynecology 2001, 13:115-119

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(4) Guideline. 1996 Blackwell Science Ltd. British Journal of Hematology 95: 21-26.

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THROMBOEMBOLISM IN PREGNANCY

Pulmonary embolism 1-2 per 100,000 pregnancies is the major cause of maternal death in the developed world.
Deep vein thrombosis (DVT), affects 1-2 of 1,000 pregnancies.

Risk factors:

- Age (double with age > 35)
- Obesity
- Operative deliveries (Cesarean section increase the risk 3-5 times)
- Previous thromboembolism (5-12%)
- Prolonged bed rest/immobilization
- Preeclampsia after delivery (increase the risk 3-5 times).
- Gross varicose veins
- Parity greater than 4 in pregnancy (increase the risk 3 times but not post partum)
- Thrombophilia increase risk at least 3 times and caused 50% of cases of DVT and pulmonary embolism in pregnancy

Congenital Thrombophilia:

Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden
Prothrombin gene mutation

Acquired Thrombophilia:

Antiphospholipid Syndrom (Lupus anticoagulant, anticardiolipin antibodies, anti-β2-glucoprotein)

- Excessive blood loss
- Paraplegia
- Sickle cell disease
- Inflammatory bowel disease and urinary tract infection
- Dehydration

D V T:
Symptoms:

Left sided 85% and the ilio-femoral 72%
Leg pain or discomfort, swelling, tenderness and/or redness
Increase temperature, edema, lower abdominal pain
Elevated white cell count
Ultrasound Doppler

Low level of D-dimer suggest that there is no venous thromboembolism

DIAGNOSIS AND WHO TO TREAT:

Golden standard venography 3140 μGy (Max recommended exposure in pregnancy = 50,000 μGy)
Compression Duplex Ultrasound Doppler (DUS), Magnetic Resonance (MRV)
DUS is excellent for proximal DVT, but may miss distal DVT

If ultrasound is negative and high levels of clinical suspicion excist, the patient should continue anticoagulation and ultrasound repeated (in one week). If repeated testing is negative, anticoagulant treatment should be discontinued. When iliac vein thrombosis is suspected (bachpain and swelling of intire limp) MR or contrast venographi scould be considered.

MRV should be avoided in 1 trimester because of lack of experience.

PULMONARY EMBOLUS (PE):

Symptoms:

Dyspnoea, Tachypnea and tachycardia (important) sometimes chest pain,hemophysis, fever, panic, cyanosis, and signs of DVT.

Diagnosis:

Ventilation – perfusion lung scan (V/Q) and compression Duplex chest X-ray Doppler ultrasound. Ventilation scan only has to be done if there is abnormal perfusion scan. A normal V/Q scan virtually exclude pulmonary embolus. If a scan shows low probability and ultrasound studies of legs Doppler are positive, PE is diagnosed.

Even if the V/Q scan shows low probability and leg Doppler is negative, continue anticoagulation treatment and repeat testing in one week computed tomography pulmonary angiography (CTPA)) (golden standard) and spiral CT should be considered (relative large amount of radiation to the fetus). VQ scan slightly increase risk of childhood cancer compared to CTPA (1:280.000 versus 1:100.000.

If high suspicion, therapy and serial testing.

Chest X-ray often normal (50%) but atelectasis, wedge-shaped infarction and pleural effusion can be seen.
CTG, ECG is usually normal except for a sinus tachycardia. Right axis deviation, right bundle branch block, peaked P-waves in lead II due to right atrial dilation and SI, QIII, TIII may be seen.

White cell count increases
Artery blood gas and/or oxygen saturation decreases.
Echocardiography only 30-40 % will have abnormalities (increased right ventricel, decreased right ventricel function and tricusspidal regurgilation.
In massive PE unfractionated heparin is the prefered treatment and thrombolytic therapy or surgical, embolectomi should be considered.
A diagnose of DVT may indirectly confirm the diagnose of PE and since anticoagulant therapy is the same, further investigation may not be necessary.

Drugs:

Heparin does not cross, the placenta, but can cause osteoporosis and rarely thrombocytopenia. These side effects has not been seen in pregnant women on LMWH. The platelet count should be monitored after 5-10 days and then on a monthly basis to detect heparin-induced thrombocytopenia (HIT) $\geq$ 50 % decrease, which is associated with further thrombotic complications. If Heparin given the last 100 days, HIT can develop after 1-3 days. A mild early form with mild thrombocytopenia > 65 is without risk.
Pregnant women who develop heparin-induced thrombocytopenia and require continuing anticoagulant therapy should be managed with the heparinoid, danaparoid sodium or factor Xo inhibitors: ie fundaparmix under special advise.

Osteoporosis after one-month treatment, lower risk with LMWH.
Allergi > 2 %, most local site

Warfarin: Crosses the placenta, no teratogenic effect before the 6 weeks of gestation. Embryopathy most often affected bone and cartilage (nasal and limb hypoplasia, chondrodysplasia). More seldom CNS maldeformation and optic nerve injury. .
The period of risk is between 6 and 12 weeks of gestation so no risk at conception. The risk may depend on dose (increase if dose > 5 mg/day). There is a significant risk of maternal (retroplacental) and fetal (intracerebral) bleeding when used in the third trimester, and particularly after 36 weeks gestation.
No anticoagulation in milk.

Treatment:

- In generel there should be *no difference in the treatment of DVT or pulmonary embolus* during pregnancy. Therapeutic anticoagulant should be continued during pregnancy and at least 6 weeks postnatal and until at least 3 months of treatment has been given in total. If DVT/PE occurs postpartum and if no other risk factors then, treatment should be 3 months for DVT and 6 months for PE.

- In clinically strongly suspected DVT and/or PE treatment Heparin should be given until the diagnosis is excluded by effective testing (see above) unless treatment is strongly contraindicated.

- The leg should be elevated and elastic compression stocking (TED) applied to reduce oedema.

- Mobilization should be encouraged.

- Duration of Treatment: Therapeutic doses of LMWH remaining of pregnancy and normally 6 weeks after delivery.

Before anticoagulant treatment is commenced, hemoglobin, creatinin, APTT, INR, platelets. Arterial puncture in case of suspect pulmonary embolus. electrolytes and liver function test (to exclude renal or hepatic dysfunction which are cautious). P-Heparin in case monitoring is needed during treatment.

Antenatal prophylactic and therapeutic doses of low-mulecular-weight Heparin			
Prophylaxis	Enoxaparin 1000 units/mg (Klexane)	Dalteparin (Fragmin)	Tinzaparin [B] (Innohep)
Normal body weight (50-90 kg)	40 mg daily	5000 units daily	4500 units daily
Body weight < 50 kg	20 mg daily	2500 units daily	3500 units daily
Body weight > 90 kga	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Higher prophylactic dose	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly

Therapeutic dose	1 mg/kg 12-hourly	90 units/kg hourly	90 units/kg hourly
Danish recommandation	1,5 mg /24 hours		175 units/kg /24 hours in 2 dosis
[B] The dosage schedules for tinzaparin differ from the menufacturer's recommendation of once-daily dosage			

Taken from RCOG Guidelines No. 37

For LMWH, firm guidelines regarding the need for monitoring have not been established but intermittent monitoring by anti-factor Xa assay 2-3 hours after LMWH injection starting in the second trimester is recommended by some. "The aim is a plasma Anti X-A level at 0.6 – 1.0 U/mL".

Thrombophilia should be ruled out after pregnancy and one month after cessation of treatment (coagulation parameters are changed in pregnancy, e.g. low protein C).

SUGGESTED PROTOCOL FOR COMMENCING WARFARIN TREATMENT IN THE PUERPERIUM (ADAPTED FROM BRITISH SOCIETY FOR HEAMATOLOGY GUIDELINES, 1998)

Day of Warfarin Treatment	International Normalized Ratio	Warfarin Dose (mg)
First		7.0
Second		7.0
Third	<2.0	7.0
	2.0-2.1	5.0
	2.2-2.3	4.5
	2.4-2.5	4.0
	2.6-2.7	3.5
	2.8-2.9	3.0
	3.0-3.1	2.5
	3.2-3.3	2.0
	3.4	1.5
	3.5	1.0
	3.6-4.0	0.5
	>4.0	0.0
Fourth	<1.4	>8.0
	1.4	8.0
	1.5	7.5
	1.6-1.7	7.0
	1.8	6.5
	1.9	6.0
	2.0-2.1	5.5
	2.2-2.3	5.0
	2.4-2.6	4.5
	2.7-3.0	4.0
	3.1-3.5	3.5
	3.6-4.0	3.0
	4.1-4.5	Omit next day's dose then give 2 mg
	>4.5	Omit two days doses then give 1 mg

Propfylactic regime in prevention thromboembolic disease:

Therapeutic dose routine measurement of peak anti-XA only recommended in women of extremes bodyweight (less than 50 kg and 90 kg or more with complicated factors for example with renal impairment or recurrent VTF) peak anti-XA activity 3 hours post injection of 0,5-1,2 units/ml.

Life threating PTE unfractionated intravenous heparin: Loding dose 80 units/kg followed by continuous IV infusion of 18 units/kg/hour. If thrombolysis is planned the loading dose is omitted. APTT 4-6 hours after loading dose, 6 hours after any dose change and then at least daily target APTT 1,5-2,5 times average control values

Aspirin 75 mg be given when LMWH are indicated.

In spontaneous in women recicving therapeutic dose of subcutanes unfractionated Heparin carefully monitoring the APTT is required. Heparin subcutaneous discontinued 6 hours before and IV Heparin 6 hours before induction or regional anaesthecia.

Previous thromboemboli:

1. Previous thromboembolic with transient risk factors (i.e. surgery, bed rest ect). Careful observation during pregnancy.

LMWH one week before term to 6 weeks post partum (If only previous crus thrombosis observation is enough).

2. Previous idiopathic thromboemboli during pregnancy and intake of oral contraceptive, other risk factors of long duration, and congenital thrombofilia (antithrombin, protein C and protein S, factor V Leiden, prothrombin G202110 mutation, antiphospholipid antibodies: (cardiolipin antibodies, lupus anticoagulans) hyperhomocysteinaemi
   (5 mg follic acid).
3. Women in antikoagulation treatment because of previous thromboemboli.

LMWH from beginning of pregnancy to 6 weeks post partum.

Intermediate dose in case of antithrombin deficiency, homozygocity for Factor V Leidin or prothrombin G202110 mutation or a combination of 2 or more risk factors as well as first degree relative with risk factors for thromboembolic desease and severe thromboembolic events.

Thrombophilia and no case of thromboembolia, observation or LMWH:
LMWH is required in cases of antithrombin deficity, homozygocity for factor V Leiden or prothrombin G202110 or combination of 2 or more inherited risk factors.

From one week before term to 6 weeks post partum, congenital antithrombin deficiency (low risk protein S and C deficiency as well lupus antikoagulans and cardiolipin antibodies in high titer.

Anticoagulation in case of previous pregnancy complications
Antiphosfolipid antibodies and previous two abortions after 10 gestational week, IUGR, fetal death, abruption or preeclampsia.

***Amniocentesis**:*
Heparin should be discontinued the night before and resume 6 hours post amniocentesis.

Prophylaxis in patiens with mechanical heart valves:

- Heparin from 0-16 (13)/52
  Warfarin from 16-32-(36/52)
  Heparin from 32-36/52 to delivery
  Warfarin postpartum

- When changing from Heparin to Warfarin, do not D/C LMWF until INR has been therapeutic for more than 2 days. When changing from Warfarin to Heparin
  consider doing this as an inpatient.

- Consider warfarin throughout pregnancy
  particularly if the patient needs < 5 mg.

Prevention of Osteoporosis

Calcium supplementation (1,500 mg in divided doses daily), Vitamin D (800 U daily) and weight bearing exercises (e.g. walking) are recommended for women using Heparin to minimize the osteopenic effects of this drug.

Labour, epidural and Cesarean sectio:

The woman should be advised that once she is established in or thinks that she is in , she should not inject any further heparin. She should be reassessed on admission to hospital and further doses should be prescribed by medical staff.

Epidural/spinal

Therapeutic doses of LMWH are replaced by profylactic dosis 24 hours before labour.
Epidural/spinal can be applied or catheter removed 12 hours after injection of profylactic dose (or P-Heparin <0,20 klU/l).
New profylactic dose given not earlier than 2 hours before application or removel of catheter.
Warfarin should be given 24 hours after delivery and is recommended if anticoagulation is expected to be more than 6 weeks post partum.
Cesarean Section:
For delivery by elective Cesarean Section, the woman should receive a thromboprophylactic dose of LMWH on the day (evening) prior to deliver. On the day of delivery, the morning dose should be omitted and the operation performed that morning. The thrombophylactic dose of LMWH should be given three hours postoperatively (four hours after removal of the epidural catheter, if appropriate), and the treatment dose recommenced that evening.

There is an increase risk of wound haematoma following Cesarean section prophylactic heparin (around 2%) especially if given two hours before surgery.

If patients receiving therapeutic dose of LMWH, wound drains should be considered at Cesarean section and the skin incision should be closed with staples or interrupted sutures to allow drainage of any haematoma.

I. Prevention of Post-Thrombotic Syndrome

Graduated elastic compression stockings should be worn on the affected leg for two years after the acute event to reduce the risk of post-thrombotic syndrome if swelling persist. A RCT in non-pregnant patients has shown that such therapy can reduce the incidence of post thrombotic syndrome from 23% to 11%.

Treatment of Patients on Anticoagulation Who Needs Acute Surgery/CS:

(1) All such patients should have their INR reversed unless they either have a mechanical mitral valve or have a DVT/PE within the previous two months, in which case the INR should only reduced to around 2.

(2) An urgent order for 6-12 units (1 unit = 145 cc) of fresh frozen plasma (15 mls/kg) should be placed and the blood bank contacted to ensure the fastest possible delivery (thawing of 4-6 units takes 20 minutes.

(3) Two IV's should be inserted and the FFP infused at maximum speed, .(5 to 10 minutes per unit) unless the patient's cardiovascular status precludes this.

(4) Blood for STAT INR should be drawn 15 minutes after the infusion of the last FFP to document that the INR has been reversed.

(5) Bleeding or active major bleeding where instant reversal is warranted or inpatients who cannot tolerate the fluid load of FFP infusion give r-Factor VIIa: 20 μG/kg IV as bolus over 5 min (< 10 ml). It works instantly; do repeat INR after 15 minutes.

(6) If bleeding does not stop, repeat the dose every 2 hours. Repeat INR 6 hours after last dose. If > 1.5, repeat bolus r-Factor VIIa.

II. Elective Surgery

Prophylaxis for perioperative management of patients on Warfarin.

A.	Low Risk TE	Stop Warfarin 4 days (Target INR near normal). DVT prophylaxis if required for procedure. Restart Warfarin postop.
B.	Moderate Risk TE	Add Heparin 5000 s.c. bid (Enaxoparin 40 mg s.c.) 2 days prior to surgery, continued postop until INR is therapeutic.
C.	High Risk TE	Stop Warfarin 3-4 days (Target INR 1.3-1.5) Full heparinization as INR < therapeutic Stop Heparin (IV for valves) 6 hr, or LMWH (for VTE) 12 hrs prior to surgery Restart IV Heparin 12 hr postop (consult Surgeon). Continue until INR therapeutic. Restart Warfarin within 24 hr postop (consult Surgeon).
D.	Patients with low risk bleeding	Decrease Warfarin (Target INR 1.3-1.5) 4-5 days preop . Restart Warfarin postop with Heparin 5000 s.c. if necessary.

III. Antiheparin Agents

Protamine Sulfate

In the situation of Heparin overdosage, since blood Heparin concentrations decrease rapidly after administration, adjust the Protamine dosage depending upon the duration of time since heparin administration as follows:

Time Elapsed	Dose of Protamine (mg) to Neutralize 100 units of Heparin
Immediate	1-1.5
30-60 min.	0.5-0.75
> 2 h	0.25-0.375

If Heparin administered by deep s.c. injection, use 1-1.5 mg Protamine per 100 units Heparin; this may be done by a portion of the dose (e.g. 25-80 mg) given slowly IV followed by the remaining portion as a continuous infusion over 8-16 hours (the expected absorption time of the s.c. Heparin dose).

Administration:

For I.V. only: incompatible with cephalosporins and penicillins; administer slow IVP (50 mg over 10 minutes); rapid I.V. infusion causes hypotension;inject without further dilution over 1-3 minutes, maximum of 50 mg in any 10-minute period.

References:

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THROMBOPHILIA IN PREGNANCY (Inherited)

Ten to 15 percent of Western population has thrombophilia and these disorders are responsible, at least in part, for approximately one-half of cases of maternal thromboembolism related to pregnancy.

Acquired (See Antiphospholipid Syndrome page 5)
Inherited (Discussed Here)

Inherited thrombophilias are genetic conditions that increase the risk of thromboembolic disease.
During pregnancy, the thrombogenic potential of these disorders is enhanced because of pregnancy-associated changes in several coagulation factors, producing a hyper coagulable state.

- Resistance to activated protein C increases in the second and third trimesters (false positive)
- Protein S decreases, about 50 %.
- Fibrinogen, Factors II, VII, VIII, X and XII increase
- Activity of the fibrinolytic inhibitors PAI-1 and PAI-2 increases

Women should be recommended screening for thrombo-philia:
If previous thrombosis, and first degree relatives with documented thromboemboli before age 50, severe early onset preeclampsia, severe or recurrent abruption, severe IUGR < 5 percentile, fetal death after 10 weeks of gestation with placental thrombosis and/or infection. Thrombosis in the fetus.

Types of inherited thrombophilias.

The most common:
- Heterozygote for Factor V Leiden Mutation (most common)
- Mutation of the prothrombin gene (G20120A)
- Homocygosety for Methylenetetrahydrofolate reductase which tends to increase plasma homocysteine.
- Polymorphism of the PA1-gene (4G/4G)

Rarer causes:
- Antithrombin (AT) deficiency
- Protein S or protein C deficiency
- Protein S deficiency and antibodies to Protein S
- Platelet collagen receptor alpha2–beta 1 C807T.

Heterozygocity for the Factor V Leiden mutation accounts for 90-95 % of the activated protein C resistance (APC). Activated partial thromboplastin time (aPTT) – based assays serve as a screening test for APC resistance.
Heterocygosety for Factor V Leiden is highest among Caucasians 5-8 % and lowest among Asians 0,5 %.
Homozygosity for Factor V Leiden is 1 % of patient with the factor V Leiden Mutation.

Patients should be tested for thrombocytia openia associated with antiphosphollpid Syndrom (aquired thrombophilia).

Estimated prevalence of thrombophilic disorders and risk of pregnancy loss

Probability of thromboembolism in pregnant women:

	% of general population	**% of patients with first VTE**	**Risk of pregnancy VTE (OR) loss (OR)**	
Antithrombin definicy*	0.7%	1%	10-20	2-5
Protein C deficiency*	0.3%	3%	6-8	2-3
Protein S deficiency*	0.2%	3%	2-6	3-40
Factor V-Leiden heterozygous)	5%-8%	20%	4-8	2-5
Factor V-Leiden (homozygous)*/**	0.06%	1.5%	80	
Prothrombin gene mutation	3%	6%	2-4	2-9
Hyperhomocysteinemia**	5%	10%	2-3	3-7
Homozygous MTHFR C677T	10-0%	11-12%	0.7-2	0.4-3
Antiphospholipid antibodies*/**	2%	10-15%	9	
Acquired APC resistance (without FV Leiden	8-11%	24%	2-4	3-4

VTE: Venous thromboembolism.

* Established associations with fetal death
* Established associations with preeclampsi

APC is thus not the same as Factor V-Leiden, but is very good screening test to identify those who may have Factor V-Leiden as it is cheap to do.

Pregnancy Related Thrombosis in Women with Inherited Thrombophilia?

Deficiency	Risk if no personal or Family history of Thrombosis, percent	Risk if personal or family history of thrombosis, percent
Antithrombin (ATIII) deficiency	≤ 3	11 to 60
Protein C	≤ 3	3 to 19
Protein S	0 to 7	0 to 22

Adapted from data in Bonnar, J Am J Obstet Gynecol 1999, 180:734.

High Risk of VTE:

- Life long Anticoagulation Treatment
- Antithrombin deficiency
- Homozygotes for the Factor V Leiden mutation
- Homozygous for the prothrombin G20210A mutation
- Double heterozygotes for Factor V Leiden and prothrombin G20210A mutations

Intermediate Risk of VTE

- A previous thromboembolic event and either congenital thrombophilia or familiar predisposition for VTE
- Heterozygote protein S and C deficiency
- Homozygote for Factor V-Leiden or prothrombin G2021A, mutation
- Combined heterozygote
- Heterozygote Factor V-Leiden or Prothrombin G2021A mutation with previous thrombosis
- Homocysteinemia despite folic acid/B6/B12 supplement

Low Risk of VTE

- Heterozygote Factor V-Leiden or Prothrombin G2021A mutation without previous thrombosis
- Homocysteinemia without folic acid/B6/B12 Supplement

Additional Risk Factors

Caesarean Section and immobilization, BMI > 30 (age > 35 years, para 4, multipregnancy, preeclampsia)

Prophylactic Heparin should be considered in case of previous severe preeclampsia intrauterine fetal death, severe IUGR or abruption of the placenta.

Treatment: See Thromboembolism and Prophylaxis page 101.

References:

(1) James, AH. Preventure and management of veneous thromboembolia in pregnancy. Am J Med 2007;1280:26-34.

(2) Kujovich JL. Thrombophilia and pregnancy complications. Am J Am J Obstet Gynecol 2004:191:412-24

(3) Nielson-Pierce C. Handbook of Obstetrics Medicine. 2002 Edition.

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THYROID DISEASE IN PREGNANCY

THYROID FUNCTION DURING NORMAL PREGNANCY

Serum TBG concentrations rise almost two-fold and leads to an increase in both serum total thyroxine (T_4) and Tri-iodothyronine (T_3) but not free T4 and T3 (See normal lab values).

TSH falls in the first trimester but may rise in early pregnancy and increase in the third trimester. Similarly the normal range for free (T_3) and (T_4) are reduced in the end of pregnancy (see normal lab values).

HYPERTHYROIDISM

Transient subclinical hyperthyroidism occurs in 10-20 per cent of normal pregnant women during the period serum HcG concentration is the highest. Hyperemesis gravidarum is often associated with biochemical hyperthyroidism. Trophoblastic hyperthyroidism occurs in about 60 per cent of women with hydatidiform mole or chorion carcinoma.

Hyperthyroidism complicating pregnancy occurs in 0.2% of pregnancies most often (95%) Graves' thyroid disease (autoimmune disease with stimulating antibodies). Other causes are toxic adenomas and subacute lymphocystic thyroidism. Some antibodies can inhibit fetal thyroidism.

Autoimmune thyroid disease is common in pregnancy. The thyroid peroxidase antibodies (TPA) or antibodies against thyreoglubin is associated with a significant increase in miscarriage rate.

Pregnancy complicated with poorly controlled hyperthyroidism is associated with increase rate of spontaneous abortion, preterm delivery, IUGR, stillbirth, preeclampsia, congestive heart failure.

Crisis are seldom: Precipitated by , infection and preeclampsia.

Exacerbation may occur in the first trimester and improvement in the last half of pregnancy (TSH receptor stimulating antibodies may fall).

Diagnosis

Raised T3 and T4 and TSH fall (see normal lab values) present of TRAb and goiter and present of TRAb autoimmunity.

Normally diagnosed before pregnancy but can be revealed in pregnancy (most often take place in the first or the beginning of the second trimester).

Symptoms

Exophthalmos (may occur before hyperthyroidism) tremor, lid lag, weight loss, tachycardia.

Treatment

The goal is to keep the mother euthyroid with free T3 and T4 in the high normal range using the lowest drug dose.
Control TSH, free T3 and T4 every 4 weeks.

Thionamides

Both prophylthiouracil (PTU) and Methimazole (MMI) cross the placenta and can cause fetal hypothyroidism and goiter. PTU has generally been preferred because it has not been associated with fetal scalp defects – aplasia cutis or choanal or esophageal atresia which very rarely has been seen with MMI. PTU has a shorter halflife and more bound to albumin which may result in less fetal hypothyroidism.

Women on maintenance dose of MMI need not be switch to PTU in pregnancy.

Newly diagnosed thyrotoxicosis should be aggressively treated with PTU 450 mg for 4-6 weeks before reduction in dose.

Doses of PTU $\leq$ 150 mg/day or MMI $\leq$ 45 are unlikely to cause problems in the fetus. And these doses are safe for breastfeeding (only 0.07% of the maternal dose is consumed by the fetus). If

higher dose, the thyroid function should be checked in the neonate.

Combined therapy with Thyroxin "block and replace therapy" has no place (fetal thyroidism).

β-blockers

Often used in early management for symptoms and discontinued once there is clinical improvement, usually after 3 weeks.

Can occasionally cause IUGR, hypoglycemia, respiratory depression and tachycardia.

Surgery

Rarely indicated. Usually reserved for those with dysplasia or stridor and those who has or develop allergies to antithyroid drugs (1-5%). Best performed in the II trimester, if necessary. May be associated with increased risk of abortion and preterm .

Radioactive Iodine

Contraindicated in pregnancies and 4 months after treatment.

Fetal and neonatal Grave´s disease

Graves disease occurs in 0,2 % of mothers and 1-5% have neonatal hyperthyroidism due to transplacental transfer of TSH receptor-stimulating antibodies (TRAb) (TSHR-SAb).
Half life is long (Weeks) and symptoms seen up to 6 weeks post partum.
Values five-fold and more are predictive. Low < 2 U/l minimal risk.

Symptoms: High fetal heart rate (> 160 beats/min, fetal goiter, fetal hydrops, pretem delivery, advanced bone age, IUGR fetal deaths and craniosynostosis are manifestations of fetal thyrotoxicosis (seldom). Fetal blood sampling for thyroid function test may be considered. Propylthiouracil and Methimaxol as well as betablockers (Propranolol) may be given to mothers to treat fetuses who have severe tachycardia or very poor growth. The pediatrician should be informed whenever there is a history of maternal thyroid disease without treatment, as the mortality rate of the newborn is almost 15%.

The treatment is only needed for a few weeks.
NB! In case of unexplained fetal tachycardia and goiter, TRAB should be measured.
In case of struma and treatment with antithyreoid medicine which can block the infants thyreoid gland. The infant can develop slight but transiant hypofunction. If the mother has TRAb antibodies the baby can later develop hyperthyroidism.
Yodine uptake: recommended dose 2250 µ/d. The prevalende: overt (0,3-0,5%), subclinical 2-3%

HYPOTHYROIDISM

IUGR, pretern birth, abortion, congenital anomalies, (10=20%) perinatal mortality and neuro-psychological impairment. Even a free T4 concentration below 10th percentile caused an increased risk for slightly lower I.Q.

Overt hypothyroidism are rare because of anovulation and first trimester abortion. The fetus depending on maternal thyroid hormone until thyroid fetal function begins around 12 weeks of gestation.

Women with thyroid autoimmunity and euthyroid are at risk of developing hypothyreodism and should be monitored by TSH.

Symptoms:

Lethargy, tiredness, hairless, dry skin, constipation, carpal tunnel syndrome, fluid retention and goiter

Cases:

Most common Hashimoto's thyroiditis or and Grave's disease. Others are atropic thyoriditis or iatrogenic (thyroidectomy, radioactive therapy) and related to drugs (iodine, lithium anti-thyroid drugs).

Diagnosis:

Low free T4 and raised TSH (see normal lab values) suggest primary hypothyreodisme, overt if free T4 are clearly below normal and subclinical if free T4 is normal..

Treatment:

The goal of therapy is to normalize the mother's serum TSH concentration, low in the normal range (<2,5 mUI/l in first trimester and <3,0 in the rest of the pregnancy). Free T3 in the upper 1/3 of the normal range.
The dose need often to be adjusted as early as 4-6 gestation week and may require a 30-50% increase in dose. Full repracement thyroxine dose 2,0-2,4 µg/kg.
Small amount of thyroxine cross the placenta but no risk for thyrotoxicosis of the fetus. Most have maintenance dose of 100-150 µg/day. Starting dose normal 100-150 µg/day

NEONATAL/FETAL HYPOTHYROIDISM

Very rare. Most cases caused by agenesis or dysgenesis of the fetal thyroid, congenital ages = hormonogenesis, or iodine deficiencies in endemic areas. And woman with atrophic thyroiditis due to transplacental TSH receptor-blocking antibodies (TRAb) causing transient fetal goiter.

POSTPARTUM THYROID DYSFUNCTION

Incidence 5-10% and in up to 25% with type 1 diabetes, also high if previous Grave's disease and high antibody peroxidase concentration. Most common in families with history of hypothyroidism and type I diabetes and those with thyroid peroxidase (antimicrosomal) antibodies in whom 50-70% will develop postpartum thyroiditis and one third develop permanent hypothyroidism within 4 years.

Two patterns can be defined:

Subacute lymphocytic (postpartum) thyroiditis and postpartum exacerbation of chronic lymphocytic (Hashimoto's) thyroiditis.

The clinical presentations are:

(a) Monophasic: producing transient hypothyroidism (40%) or hyperthyroidism (40%) or
(b) Biphasic (20%) producing hyperthyroidism and the more prolonged hypothyroidism (4-8 month postpartum) but permanent hypothyroidism in 3-4%.

Recurrent risk is high in subsequent pregnancies.

Differential Diagnosis:

Flare up of Grave's disease .
Distinguish postpartum by iodine or technetium scan high uptake in Grave's disease) and absent thyroid stimulating antibodies in postpartum thyroiditis.

THYROID NODULE

About 1% of woman and up to 40% malignant (most often papillary carcinoma) especially if tumor are fixated, rapid growth of painless tumor (very sudden onset suggest bleeding into a cystic lesion), solid lymphadenopathy, voice change, Homer's syndrome.

Diagnosis:

Should be evaluated in the same way as if the woman is not pregnant. Radionuclide scanning is contraindicated.
Thyroid function test should be performed to exclude a toxic nodule or Hashimoto's thyroiditis.

A raised Thyroglobulin titre (-100 μg (L) is suggestive of malignancy.

Ultrasound:

Cystic lesions more likely to be benign.

Surgery in case of malignancy performed in the II or III trimester with Thyroxine given postoperative to suppress TSH since residual tumor is usually TSH dependent.

References:

(1) Albalovich M et al. Management of Thyroid Dysfunction durin g Pregnancy and Postpartum: An Endocrine Society Clinial Practice Guideline. J.Clin. Endocrinol. Metab. , 92 (suppl. 8) s. 1-47, 2007

(2) Nelson-Piercy C. Handbook of Obstetric Medicine. Second Edition, By Martin Dunitz, Ltd., published in the United Kingdom in 2002.

(3) www.uptodate.com 2007

TOXOPLASMOSIS

Toxoplasmosis: Toxoplasma gondii; Obligates intracellular parasites. 10-30% previous infected. Killed > 65^0C and < -12^0C 24 hours. Microwave not secure. Incubation 5-21 days.
Comes ultimately from cats.
Only 10% of infected women develop symptoms (glandular influenza/mononucleosis like symptoms)
In most cases parasitiemia is less than 3 weeks.
IgG antibodies increase 2-3 weeks after infection, if positive, IgM normally appear within the first week and generally decline within one month/months but may persist for years.
Discuss with laboratory if in doubt.

Risk of Fetus: Prevalence of congenital toxoplasmosis is 1-10 per 10.000 births. 30-50% gets infected.
Transmission increases with gestational age. (First the placenta is infected and later toxoplasmosis is transferred to the fetus).
Transmission is possible in 1-15% in the first trimester resulting in 40% abortion or death and severe hydrocephalus and growth retardation.
Second trimester: 30% are infected in the second trimester 10% being severely damaged.
Third trimester: 60-90% are infected but only few percent are affected. The infection may be be latent and reactivated later (chorioretinitis, hearing loss and mental retardation).

Symptoms and Sequelae:
Symptoms: 1/3 lymphfadenit, 1/3 tired and only ¼ seeks edical help without the diagnosis has been established.

Less than 10% have symptoms as newborns (The classic triade: hydrocephalus, intra-cranial calcification, chorioretinitis, and most have fever, jaundice thrombocytopenia, hepatosplenomegaly). These cases have high mortality and morbidity with mental retardation and blindness.

Mild and subclinical infection will give sequelae (minimal brain damage) and 1/3 will later need special help in school.

Diagnosis: Negative IgG/IgM not infected previously, but repeat after 10-14 days if mother has been subjected to infection.
IgM > 300 iu/ml suggest active infection. Positive IgM up to 6-8 months, but can persist for years. IGM-positives should always undergo confirmatory tests in a reference atory. IgA suggest infection.
If negative IgG and positive IgM repeat after 2 weeks if unchanged possible unspecified activity.
IgM combined with increased IgG suggest a recent infection (3 weeks apart). High IgG avidity rule out infection acquired in the recent 3-4 months. Low IgG avid test indicate recent infection, but can persist beyond 3 months after infection.

Amniocentesis with PCR analyses the best method for detecting fetal infection (four weeks after infection), probably less reliable before 14 weeks.

Current practice is to advice all women to have amniocentesis (unless infection is acquired late in pregnancy), and to suggest termination only if there is a diagnosis of fetal infection and detection of abnormalities in ultrasound.

Start treatment if IgA or IgM are positive. If PCR negative in NS blood, negative IgM and IgA the infant is possibly not infected, but test again after 3, 6, 9 and 12 months.

Ultrasound: Ventriculomegaly most common, cerebral calcification (Most often normal neuro- developmental outcome if seen alone), hepatomegaly, hyperechoic foci within the liver, pericardial or pleural effusion/ ascites/hydrops placenta megaly.

Treatment: Spiromycin (Rovamycin 1 x 3) (does not cross the placenta well) 1 g x 3 until the diagnosis has been confirmed and the rest of the pregnancy This caused 60% reduction in

transmission rate. Some stop treatment with Spiramycin if confirmatory tests show no fetal infection.

If infected: 3 weeks course with Spiramycin and then 3 weeks with Pyremetacin and Sulfodiazins

All infected children should be trated for one year.

Leucovorin (folic acide) (10-25 g/day/PO) to prevent bone marrow suppression.

Re-infection can occur but does not seem to result in congenital transmission.

Prevention: Do not eat undercooked or raw meat (swine and lamb).
Avoid contact with cat excrements.
Wash or peeling fruits and vegetables.

Maintaining good kitchen hygiene and hand washing.
Use gloves when gardening.

References:

(1) Montoya JG, Liesenfeld o. Toxoplasmosis. Lancet 2004; 363(9425):1965-76.

(2) www.Infpreg.com

(3) www.uptodate.com 2007

TRAVEL AND VACCINATION

For a pregnant woman and her fetus, health risks increase when traveling. The first three months are of particular concern for the fetus and travel during the final stage beginning with the 35th week is also risky. Travel to developing countries is associated with increased morbidity in pregnant women primarily due to exposure to infectious diseases such as malaria (throughout pregnancy) and hepatitis A (in the third trimester).

In advising pregnant travelers, it is worthwhile first reviewing CDC's current and detailed recommendations in "Health Information for International Travel 2003-2004", Chapter 56, Pregnancy, Breast Feeding and Travel.

These recommendations also include issues related to breast feeding women who travel.

Problems associated with various modes of travel:
Most foreign airlines do not allow pregnant women to travel after 35 weeks' gestation; for domestic airlines the limit is 36 weeks. Changes in clotting factors and venous dilation during pregnancy put pregnant travelers at risk for superficial and deep thromphlebitis, especially on long flights. Frequent walks around the cabin and stretching exercises may help. Pregnant women should also drink large amounts of non-alcoholic beverages to compensate for water loss due to the extremely low humidity of pressurized flights. Sitting for prolonged periods in a car can also increase the risk of thromboembolism in a pregnant woman; car travel should be limited to a maximum of 6 hours per day. Sea travel can exacerbate the nausea and vomiting associated with pregnancy, particularly in the first trimester. Most cruise lines will carry pregnant women up to the seventh month.

High Altitude
Pregnant women should avoid altitudes > 4,000 meters (13,123 feet). In late stage or high risk pregnancy, altitudes of > 2,500 meters (8,200 feet) should be avoided.

Prevention of Malaria:

Pregnancy is associated with increased susceptibility to malaria. If possible, stays in high risk areas should be avoided. If chemoprophylaxis is necessary and the region(s) visited do not report chloroquine resistance, chloroquine is appropriate and safe throughout pregnancy. For unavoidable travel to countries reporting chloroquine resistance, mefloquine (Lariam) is considered safe during the second and third trimesters of pregnancy and the early postpartum period.

Traveler's Diarrhea:
Pregnant women should follow strict food and water precautions. They may have an increased risk for traveler's diarrhea due to decreased gastric acidity and increased transit time of food through the intestine. Fluid loss can lead to premature labour and shock.

Antimicrobial prophylaxis is not generally recommended for pregnant women. Bismuth subsalicylate (Pepto-Bismol) is contraindicated due to the risk of fetal bleeding and teratogenicity. For treatment, oral rehydration should be used for diarrhea only when necessary. If an antibiotic is needed for treatment of invasive diarrhea, azithromycin 1000 mg as a single dose or 500 mg daily for 3 days can be used. Fluoroquinolones are contraindicated in pregnancy.

Vaccinations During Pregnancy

Cholera
Inactivated bacterial
Data on safety in pregnancy are not available
Should weigh the theoretical risk of vaccination against the risk of disease.

Hepatitis A
Inactivate Virus
Data on safety in pregnancy are not available.
Should weight the theoretical risk of vaccination against the risk of disease.
Consider immune globulin rather than vaccine.

Hepatitis B
Recombinant or plasma-derived
Recommended for women at risk of infection.
Immune globulins, pooled or hyperimmune
Immune globulin or specific globulin preparations

Administer, if indicated

Influenza
Inactivated whole virus or subunit
Recommended for women after the first trimester if in an at-risk area

Japanese encephalitis
Inactivated virus
Data on safety in pregnancy are not available
Should weight the theoretical risk of vaccination against the risk of disease

Measles
Live-attenuated virus
Contraindicated

Meningococcal meningitis
Polysaccharide
Administer if indicated

Mumps
Live-attenuated virus
Contraindicated

Plague
Inactivated bacterial
Data on safety in pregnancy are not available.
Should weigh the theoretical risk of vaccination against the risk of disease.

Pneumococcal
Polysaccharide
Administer if indicated

Polio, inactivated
Inactivated virus
Administer if indicated

Rabies
Inactivated virus
Administer if indicated

Rubella
Live-attenuated virus
Contraindicated

Tetanus-diphtheria
Toxoid
Administer if indicated

Thyphoid
Inactivated bacterial (Vi polysaccharide)
Data on safety in pregnancy are not available, but administer if indicated.
Should weigh the theoretical risk of vaccination against the risk of disease.

Typhoid (Ty21a)
Live bacterial (oral vaccine)
Data on safety in pregnancy are not available, but not absolutely contraindicated.
Should weigh the theoretical risk of vaccination against the risk of disease.

Varicella
Live-attenuated virus
Administer if indicated because of unavoidable exposure.

Reference:

(1) CDC recommendations from Health Information for International Travel 2003.

(2) ACOG Committee Opinion. Immunization during pregnancy. Intl J of Gynecology & Obstetrics 81 (2003) 123-128.

(3) ACOG Committee Opinion. Inf J Gynecol Obstet 2002;76:338-39

ULTRASOUND SCREENING

Major anomalies and Aneuploid Risk Seen on Ultrasound

Structural Defect	Population	Aneuploidy Risk	Most Common Aneuploidy

	Incidence		
Cystic hygroma	1/120 EU-1/6,000 b	60-75%	45 X (80%)
Hydrops	1/1,500-4,000 B	30-80%*	21, 18,13, XXY
Hydrocephalus	3-8/10,000 LB	3-8%	13, 18, triploidy
Holoprosencephaly	1/16,000 LB	40-60%	13, 18, 18p-
Cardiac defects	7-9/1,000 LB	5-30%	21, 18, 13, 22, 8, 9
Complete atrioventricular Canal		40-70%	21
Diaphragmatic hernia	1/3,500-4,000 LB	20-25%	13, 18, 21, 45X
Omphalocele	1/5,800 LB	30-40%	13, 18
Duodenal atresia	1/10,000 LB	20-30%	21
Bladder outlet obstruction	1-2/1,000 LB	20-25%	13, 18
Prune belly syndrome	1/35,000-50,000 LB	Low	18, 13, 45X
Facial cleft	1/700 LB	1%	13, 18 Deletions
Limb reduction	4-6/10,000 LB	8%	18
Club foot	1,2/1,000 LB	6%	18, 13, 4p-, 18q-
Hydranencephaly, Gastroschisis, Bowel Obstruction and Single Umbilical Artery have minimal aneuploidy risk.			

Abbreviations: EU: early ultrasonography

B : birth
LB : livebirth
IA : infant autopsy

*30% if diagnosed ≥ 24 weeks, 80% if diagnosed ≤ 17 weeks.

Translocation and Isochromosome 21 Down Syndrome.
If both parents have normal blood chromosomes, trisomy 21 is usually presumed to have arisen (de novo), and the observed recurrent risk in a series of trisomic cases was less than 1%. Gonadal mosaicism for isochromosome 21 has been reported and recurrences of Down Syndrome are recorded, a rounded-up 1% risk of recurrence is appropriate.

When one parent is shown to carry a balanced robertsonian translocation that has given rise to a child affected by Down Syndrome, the risk of recurrence mainly depends on the sex of the carrier parent: if the mother is a carrier, the risk of recurrence at amniocentesis is 15% (closer to 10% at term due to fetal demise after 16 weeks' gestation), compared with a much lower risk of less than 5%, even less than 1%, if the father is the translocation carrier.

Down Syndrome.

The additional type of chromosome 21 usually results from nondisjunction (failure to separate during meiosis I or meiosis II). The errors are almost all of maternal origin, only 5% occurs during spermatogenesis.
In 5% the extra chromosome 21 appears to be due to an error in mitosis and not associated with increased maternal age.
Translocation trisomy 21 with a majority of new mutations are nearly always of maternal origin.
3-4% of cases of Down due to unbalanced translocation are born to a parent with a balance Robertson translocation.

Down Syndrome recurrence risks.

The risk of the recurrence trisomy 21 in children of mothers who had one liveborn affected infanat: when the mother was age under 30, the recurrence risk is 1.4%, and this figure is clearly increased above the background rate of about 0.7%. But when the mother was older, the

trisomy 21 recurrence risk is not clearly increased above the background maternal age risk.

Parent with Trisomy 21
Rarely women wiwth trisomy 21 become pregnant, and in this situation the risk of trisomy 21 in the offsprting is close to 50%. Fertillity in males with trisomy 21 is exceptional, but there are at least two well-documented reports of an affected male fathering an unaffected child.

Risk if parent or previous child has chromosome abnormality

Soft ultrasound markers in trisomy
The absence of any markers conveys a 70% reduction in Down Syndrome prior risk.

Nasal hypoplasia
Nasal hypoplasia at 15-24 weeks of gestation has been reported as a strong marker for trisomy 21. Nasal hypoplasia is present in 60-65% of the trisomy 21 fetuses defined as a nasal bone that is not visible or with a length of <2.5 mm.
Nasal bone is absent in 1,4% of the population and the reported likelihood ratio for trisomy 21 is 146 (50- to 434) for absence of the nose bone and 0.27 (0.18 to 0.40) for present of nose bone. Absence of nose bone is seen in up to 10% in African Carribbeans.

Combining nuchal translucency and age in trisomy 21 with the use of presence or absence of the nose bone increase the sensitivity to 85% and decrease of the false- positive rate to about 1%.

Absent nose bone has also been described in fetuses with fragile X.

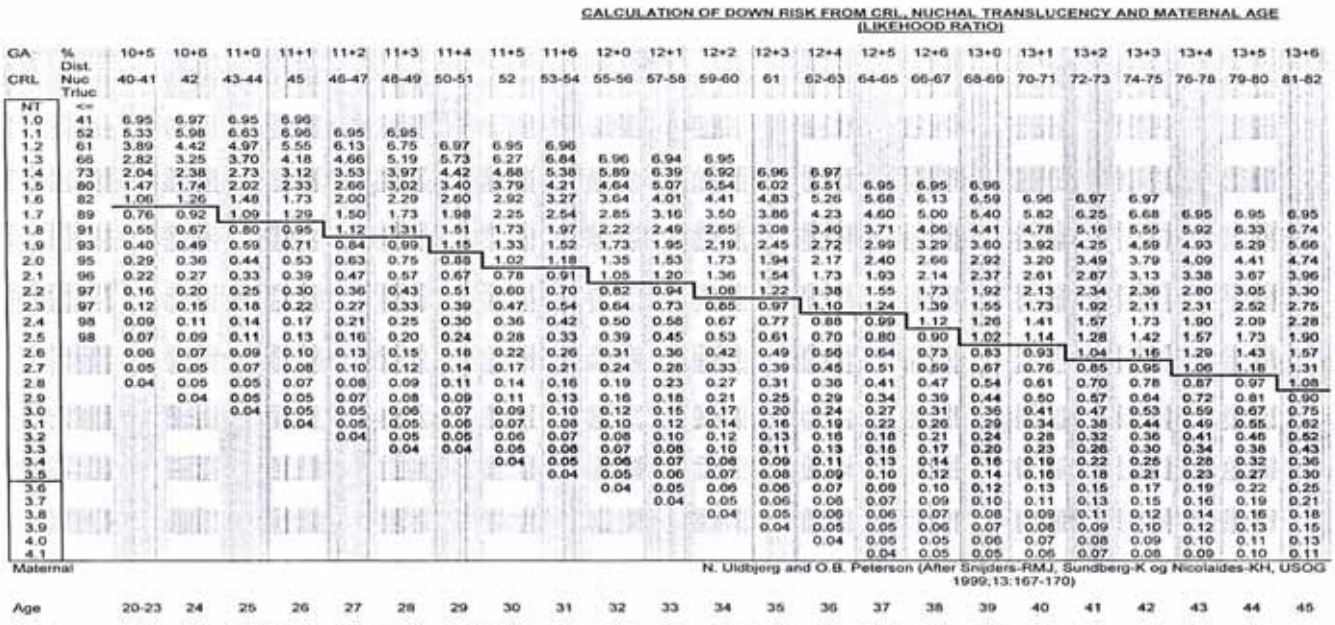
Soft ultrasound markers in trisomy
Prevalence of major and minor defects or markers in the second trimester scan in trisomy 21 and chromosomally normal fetuses in the combined data of two major series (Nyberg et al 2001; Bromley et al 2002). From these data the positive and negative likelihood ratios (with 95% confidence interval) for each marker can be calculated in the last column is the likelihood ratio for each marker found in isolation.

Sonographic Marker	Trisomy 21 %	Normal %	Positive LR	Negative LR	LR for isolated marker
Nuchal fold	33.5	0.6	53 (39-71)	0.67 (0.61-0.72)	9.8
Short humerus	33.4	1.5	22 (18-28)	0.68 (0.62-0.75)	4.1
Short femur	41.4	5.2	7 (6-9)	0.62 (0.56-0.67)	1.6
Hydronephrosis	17.6	2.6	6 (5-8)	0.85 (5.16-8.80)	1.0
Echogenic focus	28.2	4.4	6 (5-7)	0.75 (0.69-0.80)	1.1
Echogenic bowel	13.3	0.6	21 (14-31)	0.87 (0.83-0.91)	3.0
Major defect	21.4	0.65	32 (23-43)	0.79 (0.74-0.83)	5.2

LR = Likelihood Ratio

From the 11-14 weeks scan. K.H. Nicolaides 2004.

Choroid plexus cyst found in 1-2% (3-6 mm) and 95% resolves after 26 weeks. Seen in 25-30% of fetus with trisomy 18, but the vast majority will have other abnormalities. A recent study found 0.5% with aneuploidy with a risk 0.36 (0.4 to 1.3) < 36 years and 2.4 (0.06 to 12.6) > 36 years. Most do not support karyotyping as an isolated finding as the overall risk is marginal increased. If one additional abnormality is found maternal age risk increases about 20 folds.



Echogenic bowel is 0.5-1% has echogenicity of the fetal small bowel similar or greater than that of the surrounding bone. Also seen in meconium ileus secondary to cystic fibrosis, congenital infection, intra-amniotic bleeding and severe IUGR. The most prevalent chromosome abnormality is trisomy 21. The risk is 3-5 times the background risk adjusted to maternal age.

Mild hydronephrosis (3-4 to 10 mm), trisomy 21 increased risk by factor 1.6 but some don't find any increase risk as an isolated finding.

Short proximal bones: Trisomies 21, 18, trip0loidy and Turner syndrome are associated with relative shortening of the long bones. Syndactyly is accociated with triploidy, clinodactyly and sandal gap with trisomy 21 (up to 45%), polydactyly with trisomy 13, overlapping fingers, rocker bottom feet and talipes with trisomy 18.

Ventriculomegaly: (1:1000) 10-12 mm (15 mm) mild or borderline ventriculomegaly caused later severe brain abnormality in 5%, 15% mild problems later. The commonest chromosomal defects are trisomies 21, 18, 13 and triploidy. The prevalence of chromosomal defects is higher in those with mild to moderate, rather than severe ventriculomegaly. The risk in case of no other abnormalities is low.

Holoprosecencephaly: 1 per 10,000. The prevalence of chromosomal defects is about 30% and the commonest are trisomies 13 and 18. Chromosomal defects are only increased in fetuses with holoprosencephaly and extrafacial defects.

Dandy-Walker Malformation: (1:3000) Complete or partial agenesis of the cerebellar vermis and enlarged posterior fossa. The variant (partial agenesis of the cerebellar vermis without enlargement of the posterior fossa and mega-cisterna magna) is found in 4-12% of all cases of infantile hydrocephalus. 1 per 30,000. Chromosomal defects is about 40% usually trisomies 18 or 13 and triploidy.

Facial cleft. 1 per 800 live births. Chromosomal defects are found in less than 1% of babies with facial cleft. However, in prenatal series the prevalence is about 40%, most commonly trisomies 13 and 18 as the patients are pre-selected and include many fetuses with multiple other defects.

Cardiac abnormalities: Abnormalities of the heart and great arteries are found in 4-7 per 1,000 live births and in about 30 per 1,000 stillbirths. Chromosomal defect is seen in 25% of cases. The most common defects are trisomies 21, 18, 13 and Turner syndrome.

Exomphalos: 1 in 4,000. Chromosomal defects, mainly trisomies 18 and 13, are found in about 30% at mid-gestation and in 15% of neonates. The prevalence of chromosomal abnormalities is four times higher when the exomphalos sac contains only bowel than in cases where only the liver is included.

Exophageal atresia. 1 in 30,000. Chromosomal defects are found in 3-4% of affected neonates, mainly trisomy 18.

Duodenal atresia. 1 in 5,000. Trisomy 21 is found in about 40% of cases. Autosomal recessive pattern of inheritance is seen.

Urinary tract abnormalities. The prevalence of chromosomal in females is double than in males. In mild hydronephrosis, the commonest chromosomal defect is trisomy 21, whereas in moderate/severe hydronephrosis, multicystic kidneys, or renal agenesis the commonest defects are trisomies 18 and 13.

Other markers are iliac angle >90%, sensitivity 95%, false positive rate 25% in Trisomy 21

INCREASED NUCHAL TRANSLUCENCY WITH A NORMAL KARYOTYPE

Prevalence of major cardiac defects in fetuses with increased nuchal translucency thickness at 11 to 13+6 weeks.	
Nuchal translucency	**Cardiac defects**
2.5-3.4 mm	38/2236 (17.0/1000)
> 3.5 mm	95/1212 (78.4/1000)

Increased NT constitutes an indication for specialist fetal echocardiography.

In cromosomally normal fetures, the prevalence of majr cardiac defects increases expotentially with NT thickness from 1.6 per 1000 units with NT below the 95th centile 1% for NT of 2.5-3.4 mm, 3% for NT of 3.5-4.4 mm, 7% for NT of 4.5-5.4 mm, 20% for NT of 5.5-6.4 and 30% for NT of 6.5 mm or more.

Increased NT in 40% (85% in chromosomal abnormal and 40% of chromosomal normal fetuses).

Megacystis 11-14 weeks > 6 mm (1:1.500) was observed in 75% of chromosomal abnormalities mainly in trisomy 13 and in about 30% of those with normal karyotype.

In body stalk anomaly (1:10.000), NT is increased in about 85% of the cases but the karyotype is usually normal.
Skeletal defects and certain genetic syndromes such as congenital adrenal hyperplasia, fetal akinesia deformation sequence, Noonan syndrome, Smith-Lemli-Opizz syndrome and spinal muscular atrophy, appears to be substantially higher than in the general population.

Relation between nuchal translucency thickness and prevalence of chromosomal defects. , miscarriage or fetal death and major fetal abnormalities of the last column is the estimated prevalence of delivery of a healthy baby with no major abnormalities.

Nuchal Translucency	Chromosomal Defects	Fetal Death	Major Fetal abnormalities	Alive and well
< 95th centile	0.2%	1.3%	1.6%	97%
95th –98th centiles	3.7%	1.3%	2.5%	93%
3.4-4.4 mm	21.1%	2.7%	10.0%	70%
4.5-5.4 mm	33.3%	3.4%	18.5%	50%
5.5-6.4 mm	50.5%	10.1%	24.2%	30%
> 6.5 mm	64.5%	19.0%	46.2%	15%

K.H. Nicolaides 2004.

References:

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(3) Nyberg DA, Soubi VL: Sonographic markers of fetal trisomies. Ultrasound Med 20;665:2001

(4) Twining P, McHugo JM, Pilling DW. Textbook of Fetal Abnormalities. Churchill Livingstone. Harcourt Publishers Limited 2000.

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VACUUM EXTRACTION/FORCEPS

The use of forceps increases the risk of perineal, vaginal laceration and sphincter rupture.

Operative delivery (10-15%) can be decreased by continuous support during upright or lateral position and avoiding epidural analgecia.

Oxytocin in primiparus women with epidudral anaesthesia starting in the second state of labour can reduce the need for vaginal operative delivery. Operative intervention can be reduced if pushing is delayed 1-2 hours until the woman have a strong urge to push.

There is an insufficient evidens to support the hypotesis that discontinuing epudiral analgecia reduce the incidens of operative vaginal delivery.

Indication: Prolonged second stage of labour

(a) Primigravidas: More than 3 hours with a regional anesthetic or more than 2 hours without a regional anesthetic.

(b) Multiparas: More than 2 hours with a regional anesthetist or more than 1 hour without a regional anesthetic.

** if there is no maternal or fetal distress and the patient is not pushing during the whole second stage, the definition of prolonged second stage should be liberally extended.

Maternal exhaustion
Fetal distress
Contraindications to maternal expulsive efforts: cardiac disease, previous retinal detachment, maternal vascular intracranial pathology – (increased intracranial pressure is hazardous i.e. severe preeclampsia).

Special Indication:

Cord prolapse with fully dilated cervix and the baby would appear to be delivered easily.
For forceps:
Face presentation
Aftercoming head (Kjelland or Piper)
For vacuum:
Fetal distress in case of multiparas with almost fully dilated
cervix (> 8 cm)

Twin B, fetal distress when the head is still High

What instrument should be used:

Vacuum extraction more likely to fail to give cephalohaematona and retinal haemorrhage. Vacuum less likely to give maternal perinal and vaginal trauma. A five year follow-up did not show any significant different in the long term outcome for either mothers and infants whether the infant was delivered by operational vaginal delivery or Caesarean section.
Vacuum followed by forceps increase the risk for neonatal trauma.

Contraindications:

Gestational age of < 34 weeks
Suspected bleeding disturbances on the infants

Conditions: Vacuum: cervix fully dilated and membranes ruptured
Caput + 1, NOT PALPABLE OVER THE SYMPHYSIS extended caput succedeaneum often mistaken as caput is more distended than is actually the case.
Check adequacy of the pelvis (contour of sacrum, prominence of the spine, the sub-pubic angle)
Outlet forceps: Cervix should be fully dilated and caput at least at or on the perineum.
Rotation does not exceed 45% the pelvic floor.

Low forceps should be performed by an experienced operator. Skull is at station ≥ +2 and not on the pelvic ± rotation.
Mid forceps: (Vacuum is often preferable) the station is above 2 cm but head is engaged.

Place of Instrumental Delivery

If in doubt, vaginal delivery is feasible or potential fetal distress, vacuum/forceps should be performed in the operating room.

Application of the Cup:

In the midline towards the fetal occiput, 3 cm from anterior fontanelle in occiput posterior under symphysis and in other presentation place the cup posteriorly.

Applied vacuum 0.2 kg/cm = (180 mmHg and insure there is no interposition tissue). The cup can thereafter be increased to 0.8 kg/cm (600 mmHG). The same should occur in the first contraction permit no more than 3(-5) contractions with uterine contractions (20 minutes or 2 episodes of breaking of suction any trial of vacuum).

There is little evidence of increased maternal and neonatal morbibidity following failed vaginal delivery compared with immediate Caesarean section.

This rule can be broken if slow delivery is performed to protect the perineum. If no fetal distress, vacuum can be discharged and the woman can deliver the head by pushing the head alone.

References:

(1) Johansen, RH. Br.J.Obstet. 1999

(2) Operative Vaginal Delivery. RCOG Guideline No. 26, October 2005

(3) Vacca A. Handbook of vacuum extraction in obstetric practice. ISBN 0-340-54849-5.

(4) Vacuum extraction versus forceps for assisted vaginal delivery (Cochrane Review).

VARICELLA/CHICKEN POX

Most adults have had varicella zoster (VZ).
The incubation period is 13-17 days. Highly infectious (about 90%) 48 hours before the rash and lasts until the vesicles crust is over (6-10 days after first symptom). Very contagious, the whole department infected (face to face 5 minutes or indoor contact more than one hour). Previous infection can be confirmed by measuring VZV antibodies. Zoster may occur months to years after primary varicella infection.

Maternal: Varicella is most often uncomplicated, but can be more severe in adults and particularly in immunosuppresed women and pregnant women . Pneumonia occurs in up to 10%, with mortality up to 45% in the pre-antiviral era. The mortality today is less than 1% .
Mechanical ventilations can be required with up to 6% mortality. Other complications include encephalitis, generalized spread to internal organs, hepatitis, arthritis, pericarditis, glomerulonephritis, Reye's Syndrome and hemorrhagic varicella.

Transmission: 5-10% before 28 weeks, 25% from 28-36 weeks, 50-60 > 36 weeks.

Herpes Zoster: No risk for the foetus.

Congenital Varicella:

From 0-12 weeks, there is a 0.4% risk for congenital varicella and from 10-20 weeks, the symptoms of congenital varicelle are:
Low birthweight, neurological abnormalities (microcephaly, cortical atrophy, mental retardation and dysfunctional bowel and bladder sphincters.
Eye defects (microphthalmia, chorioretinitis, cataracts)
Hypoplasia of the limbs
Skin scarring in a dermatomoid distribution.

After 20 weeks very low risk for sequelae

If the mother is infected by Varicella 5 days before and 4 days after birth then there is risk for serious infection in the child. However, if the mother get VZIG only slight symptoms.
Often only slight symptoms 6-21 days before and 1-2 weeks after birth.
Very preterm babies are at high risk for severe symptoms.

Prenatal diagnosis:

Primary ultrasound after 5 weeks.
Amniocentesis with PCR for viral DNA PCR, otherwise with detection of IgM antibodies in fetal blood. However, both these tests may give false negative results.VZV antibodies of limited value.

Varicella Infection of the Newborn:

In the first 28 weeks of pregnancy and within 3 weeks of delivery, mother should receive 1,000 mg VZIG immediately after exposure if known or found to be IgG negative. If the mother present with symptoms the value of VZIG is uncertain and the patient should receive antiviral treatment in the form of acyclovir or valcyclovir.

Up to 50% infections are infected 1 to 4 weeks before delivery. Is fatal in 20-30% of infants if maternal infection occurs 5 days before the delivery and up to 2 days postpartum, but severe infection up to one month has been seen.

The infant is protected by maternal antibodies at least one month after delivery. Newborns should not be exposed to VZ if mother have not had the disease.

Management: In case of exposition in the vulnerable period VZIG to the infant and mother as well as Acyclovir.
Isolation from all other pregnant women and neonates. If delivery occurs within 5 days of infection or mother develops VZ within 2 days after delivery then the neonate should be given VZIG and Acyclovir as soon as possible.

Anti-viral therapy should be precribed for chickenpox if they present within 24 hours of the rash and if they are more than 20 weeks gestation (800 mg x 5 po).

Prophylactic: Pregnant women should not be exposed to Varicella before 20 weeks of gestation.
Women with Varicella should not be admitted to ward. The room is infected at least 1 hour.

Vacination: Avoid pregnancy in 3 months.

References:

(1) Chickenpox in pregnancy. Green-top Guideline Nor. 13, September 2007

(2) Committee Opinion: Immunization during pregnancy. Obstet. Gyneocol. 2003;101:207-12.

(3) www.infpreg.com

(4) www.uptodate.com *2007*

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