Fetal Medicine Update

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Some History

- The only way we know the fetus is alive is through the mother’s appreciation of fetal movements
- In 1821 Kergaradec used the stethoscope invented by Laennec to listen to the fetal heart
- Pinard invented the fetal stethoscope in 1895
- Till the 1950s the fetus was protected in his own spa.
More History

• 1877 ➔ Amniocentesis for amnio-reduction

• 1953 ➔ Amniocentesis for Rh isoimmunization

• 1961 ➔ Liley chart & IUT

• 1966 ➔ Culture fetal cell from amniotic fluid

• 1968 ➔ CVS

1960s ➔ Maternal Fetal Medicine began to emerge
Recent History

• 1972 ➔ US guided amniocentesis

• 1973 ➔ fetal blood sampling (Hobbins)

• 1975 ➔ US guided CVS

• 1975 ➔ IUT intra-peritoneal

• 1981 ➔ IUT intravascular

• 1988 ➔ Fetoscopic guided Laser occlusion for TTTS (De Lia)

1991 ➔ 1st International Congress of Perinatal Medicine
Landmarks in Fetal Medicine

• Ultrasound technology
• Management of red cell isoimmunization
• Nuchal translucency and screening for chromosomal abnormalities
• Prenatal genetic testing
Ian Donald is the father of OB Gyn Ultrasound

- First static ultrasound machine was developed
- Very large and heavy – Dinosaurograph
- Early gestational sac, placenta previa, molar Pregnancy could be visualized

Donald in action with the Mark 3 Diasonograph in 1960
Campbell using the NE4102, a successor to the Diasonograph with solid state components. The machine remained very large but when the operator stood, the probe could be skimmed across the surface of the abdomen to speed the scanning process.
Breakthroughs in Fetal Medicine

Treatment of red cell Isoimmunization is one of the first diseases where in-utero diagnosis and management was started

- **Intraperitoneal transfusion**: Liley 1959 - under x-ray
- **Percutaneous fetal blood transfusion**: Liley 1967
- **Fetoscopic fetal transfusion**: Rodeck 1981
- **Cordosentesis**: Fetal blood and platelet transfusion, Nicolaides 1986
Rh-Isoimmunization

At the time of delivery exposure of the mother’s blood to fetal RBCs which contain “D” may result in the formation of antibodies.
Prevention of Iso-immunization

- If Rhogam is given antenataly: the risk of sensitization is reduced from 2% to 0.2%
- If Rhogam is given postnataly: the risk of sensitization is reduced from 15% to 2%

In developed countries: the prophylaxis with rhesus immunoglobulins has decreased the incidence of Rh-hemolytic disease from 45 per 10 000 total births (live births and stillbirths) to 10.2 per 10 000 total births.
Why the Disease was not Eradicated?

1) Other Red Blood Cell Antigens

The following antibodies ARE associated with HMD:

- Rh: D, E, c, C, C\(^w\), e
- Kell: K\(_1\), Kp\(^a\), k, Js\(^a\), Js\(^b\)
- Duffy: Fy\(^a\)
- MNS: M, S, s, N
- Kidd: Jk\(^a\)

2) Missing the dose/ adequacy of the dose
In subsequent pregnancies, passage of fetal RBCs across the placenta can lead to an exaggerated response of antibody production.

The antibodies freely cross the placenta, leading to hemolysis of fetal RBCs.

Antenatal: anemia
Postnatal: jaundice
LILEY'S CURVE
Suggested management after amniocentesis for ΔOD 450

Serial Amniocentesis

- **Lily zone I**
  - **Lower Zone II**
  - Repeat Amniocentesis every 2-4 weeks
  - Delivery at or near term

- **Upper Zone II**
  - Repeat Amniocentesis in 7 days
    - Hct < 25%
      - Intrauterine Transfusion
    - Hct > 25%
      - Repeat Sampling 7 to 14 days
      - Intrauterine Transfusion

- **Zone III**
  - Hydramnios & Hydrops
    - < 35 to 36 weeks And Fetal lung immaturity
      - Intrauterine Transfusion
    - > 35 to 36 weeks Lung maturity present
      - Delivery

**Suggested management after amniocentesis for ΔOD 450**
LILEY'S CURVE

Disadvantages

- Multiple procedures are needed
- Indirect test for fetal anemia
- Not accurate for fetuses under 28 weeks

<table>
<thead>
<tr>
<th>ZONE OF LAST SAMPLE</th>
<th>NUMBER OF WOMEN</th>
<th>RATE OF INACCURATE PREDICTIONS (%)</th>
<th>RATE OF LIFE-THREATENING INACCURACY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>253</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>530</td>
<td>8.9</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>314</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>1097</td>
<td>5.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>
Fetal blood sampling/ transfusion

The gold standard for detection/ treatment of fetal anemia

Complications:

- Fetal Loss 2.7%
- Bleeding from puncture site 23- 53%
- Bradycardia 3.1- 12%
- Feto-maternal hemorrhage 65.5% (ant placenta)
  16.6% (post placenta)
- Infection and abruptio placentae Rare
Ultrasound and Fetal Anemia

- Hyperdynamic circulation
- ↑ velocity of blood flow
Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses.


MY MENTOR
Modern management of the RhD-sensitized pregnancy

Monthly Maternal Indirect Coombs Titre

- Exceeds Critical Titre
  - Paternal Rh Testing
    - Rh Positive
      - Amniocentesis for RhD antigen status (or ffDNA)
        - Fetus RhD positive
          - Weekly MCA-PSV
            - > 1.50 MOM
              - Cordocentesis or Deliver
            - < 1.50 MOM
              - Continue MCA-PSV
        - Fetus RH D Negative
          - Serial Amniocentesis
      - Fetus RH D Negative
    - Rh-negative
      - Routine Care

- Below Critical Titre
  - Routine Care

ffDNA
KFSH&RC Experience in Isoimmunization

The program started in the late 80s, first program in Saudi Arabia.


Can a single measurement of amniotic fluid delta optical density be safely used in the clinical management of Rhesus-alloimmunized pregnancies before 27 weeks' gestation? Feryal Rahman; Laura Detti; Tulin Ozcan; Rubina Khan; Sumana Manohar and Giancarlo Mari. Acta Obstetricia et Gynecologica Scandinavica, Volume 77, Issue 8, Page 804-807, Aug 1998
# KFSH&RC Experience in Isoimmunization Between 1996-2003

A total of 186 fetuses from 185 pregnancies of 122 patients, received 853 transfusions.

<table>
<thead>
<tr>
<th></th>
<th>Hydrops</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>(n = 146)</td>
<td>(n = 40)</td>
</tr>
<tr>
<td>Gestational age (weeks) at first IUT</td>
<td>22 (4.47) $^$</td>
</tr>
<tr>
<td>Hemoglobin (g/dL) at first IUT</td>
<td>7.9(2.62) *</td>
</tr>
<tr>
<td>Number of IUTs</td>
<td>5 (1.96) $^{\infty}$</td>
</tr>
<tr>
<td>Survival</td>
<td>142 *(97.3 %)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td></td>
</tr>
<tr>
<td>fetal</td>
<td>2 *(1.4%)</td>
</tr>
<tr>
<td>neonatal</td>
<td>2 (1.4%)</td>
</tr>
</tbody>
</table>

IUT, intrauterine transfusion
Data are n (%) or median (standard deviation)
*P < 0.0001
§P < 0.05
$^{\infty}$ P < 0.01

*Forty nine (5.7%) cesarean sections were done due to fetal distress following the procedure.*
Challenging Case:
Rh Isoimmunization with Glanzmann Thrombasthenia

1\textsuperscript{st} pregnancy IUFD hydrops
2\textsuperscript{nd} pregnancy: 6 intrauterine transfusions with pre-procedure platelets transfusion and Trenaxemic acid, IOL and SVD at 37 weeks
3\textsuperscript{rd} pregnancy: severe intraabdominal bleed following intrauterine transfusion, found to have antiplatelet antibodies.

With modern management: only 3 transfusions were needed.
Innovations in Fetal Medicine

History of Nuchal Translucency

The skin is deficient in elasticity giving the appearance of being too large for the body. The face is flat and the nose is small.

Observations on an ethnic classification of idiots

Langdon Down 1866

Langdon Down 1828-1896
Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy

K H Nicolaides, G Azar, D Byrne, C Mansur, K Marks

April 1992

Abstract

Objective—To examine the significance of fetal nuchal translucency at 10-14 weeks' gestation in the prediction of abnormal fetal karyotype.

Design—Prospective screening study.

Setting—The Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London.

Subjects—827 fetuses undergoing first trimester karyotyping by amniocentesis or chorionic villus sampling.

Main outcome measure—Incidence of chromosomal defects.

Results—The incidence of chromosomal defects was 3% (28 of 827 cases). In the 51 (6%) fetuses with nuchal translucency 3-8 mm thick the incidence of chromosomal defects was 35% (18 cases). In contrast, only 10 of the remaining 776 (1%) fetuses were chromosomally abnormal.

Conclusion—Fetal nuchal translucency $\geq 3$ mm is a useful first trimester marker for fetal chromosomal abnormalities.

Introduction

In the second and third trimesters of pregnancy there is a high association between fetal nuchal cystic hygromas or nuchal oedema and chromosomal abnormalities (table 1). This ultrasound screening study examines the possible significance of abnormal nuchal fluid in the first trimester as a marker of chromosomal abnormalities.

Patients and methods

During 22 months (January 1990 to October 1991) 827 women with viable pregnancies were referred to our centre for first trimester fetal karyotyping because of advanced maternal age, parental anxiety, or a family history of a chromosomal abnormality in the absence of balanced parental translocation. The median maternal age was 38 years (range 22-47). Gestational age, calculated from the last menstrual period and confirmed by measuring the fetal crown-rump length, was 10-14 (mean 11) weeks.

Transabdominal ultrasound examination (curvilinear 5 MHz transducer; Aloka 650 CO Limited, Tokyo) was performed to obtain a sagittal section of the fetus for measuring crown-rump length and the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine (figure). Care was taken to distinguish between fetal skin and amnion because at this gestation both structures appear as thin membranes.

Ultrasonic appearance of subcutaneous nuchal translucency. Both skin and amnion appear as thin membranes (top). In some cases translucency extends over wide area of fetus but most prominent behind neck (bottom).
Risk (%) vs Age (years)

- Nuchal translucency
- Background

Maternal age

- NT (Nuchal Translucency) increases with maternal age.
- NT decreases with maternal age.
<table>
<thead>
<tr>
<th>Study</th>
<th>Test Combination</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuckle 1991</td>
<td>Maternal age (MA)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>MA and AFP &amp; hCG</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>MA and AFP &amp; hCG &amp; uE3</td>
<td>63%</td>
</tr>
<tr>
<td>Cuckle 2001</td>
<td>MA and AFP &amp; ß-hCG</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>MA and AFP &amp; ß-hCG &amp; uE3</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>MA and AFP &amp; ß-hCG &amp; uE3 &amp; IA</td>
<td>72%</td>
</tr>
<tr>
<td>Snijders 1998</td>
<td>MA and Nuchal translucency (NT)</td>
<td>75%</td>
</tr>
<tr>
<td>Spencer 1999</td>
<td>MA and NT and ß-hCG &amp; PAPP- A</td>
<td>85%</td>
</tr>
<tr>
<td>Cicero 2001</td>
<td>MA and NT &amp; Nasal bone (NB)</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>MA and NT &amp; NB and ß-hCG &amp; PAPP- A</td>
<td>97%</td>
</tr>
</tbody>
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A New Era: Prenatal Genetic Testing
### The frequency of genetic disease

<table>
<thead>
<tr>
<th>Category</th>
<th>% of Total Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant</td>
<td>0.14</td>
</tr>
<tr>
<td>Recessive</td>
<td>0.17</td>
</tr>
<tr>
<td>X-linked</td>
<td>0.05</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>0.18</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>4.64</td>
</tr>
<tr>
<td>Genetic unknown</td>
<td>0.12</td>
</tr>
<tr>
<td>All congenital abnormalities</td>
<td>5.28</td>
</tr>
<tr>
<td>Congenital abnormalities with genetic etiology</td>
<td>2.66</td>
</tr>
</tbody>
</table>

**16 thousands Newborn / year in KSA**
Scope of the problem

• Genetic diseases are often encountered in highly consanguineous populations, such as Saudi Arabia—with consanguinity rates reaching up to 30-40% and even more in some areas.

• Typically, these diseases are incurable, and are a burden on the family and society as they survive for a variable period of time and require costly resources.

• Therefore, we adopted the notion: “prevention is the best cure”—in our case it is secondary prevention!!
Prevention is the best cure

Conception

Pre-implantation Genetic Diagnosis (PGD)

Marriage

Pre-Marital Screening & Counseling

Pregnancy

Genetic and Biochemical Testing at KFSH&RC

Pre-Natal Testing
- Amniocentesis
- CVS
- Cell-free fetal DNA

Newborn Screening

Molecular Diagnostics

Growth & Development
Approach to families with genetic diseases

**CLINICAL DIAGNOSIS ESTABLISHED**

- **Mutation identified**
  - Invasive Prenatal testing
  - Pre-implantation Genetic Diagnosis
- **Mutation not identified**
  - COUNSELING
  - Waiting Time
  - Complications
  - Which test?
  - When?
  - Normal pregnancy
  - TOP
  - Options
  - US
  - Delivery in Tertiary care hospital
  - Index case
KFSH Experience 2001-2006

411 cases in 5 years
Average 82 cases annually

From 7886 total births

Percent of procedures
Chromosomal
Genetic disease
Abnormal US
Advanced Maternal age

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniocentesis</td>
<td>70%</td>
</tr>
<tr>
<td>CVS</td>
<td>17%</td>
</tr>
<tr>
<td>FBS</td>
<td>13%</td>
</tr>
</tbody>
</table>

Overall Positive results: 14%
Miscarriage: 0.48%
KFSH Experience 2011-2014

965 cases in 4 years
Average 241 cases annually

From 5499 total births

Percent of procedures: Amniocentesis 37%, CVS 52%, FBS 11%
Overall Positive results: 30%
Miscarriage: 0.6%
Consanguineous: 81%
How can we help?

Options for testing:
- Single gene one mutation
- Single gene multiple known mutations
- Panels: NIH, Dysmorphology/Dysplasia, Renal
- Whole Exome Sequencing
- Research-base testing
Case 1: 5018096

- G3P2+0
- 1st degree relatives
- One child died from SCID, known mutation
- Presented at 15+ weeks for amniocentesis
- Results: carrier
- Referred back to local hospital for follow-up and delivery
Case 1: 5018096

- Referred back at 24 weeks with this picture
- Also: absent cerebellum, talipes, severe oligohydramnios
- Impression: ciliopathies
- Cordocentesis done at 26 weeks
- IUFD at 35 weeks
- Mutation found in the TCTN2 gene, diagnosed as Meckel Gruber
- So: 2 different genetic disease in one family!!
Case 2: 5186911

- 26 year-old, G2P1, previous normal child
- 1\textsuperscript{st} degree relative
- Aunt has 3 children affected with ? Skeletal dysplasia: gradual narrowing of the chest, death by 2 years of age
- Referred at 26 weeks with abnormalities
Case 2: 5186911

- Cordocentesis done for Dysmorphology/Dysplasia panel
- Mutation identified in PPIB gene: Osteogenesis Imperfecta Type IX
- Future reproductive options given: prenatal diagnosis versus PGD

We did not only help the small family but the extended family!!
Case 3: 750707

- 1st seen in 2013
- G6P5+0, living 2
- Ob history:
  - 1st: NIH, CS at 8 months, died at 17 days of age, no diagnosis
  - 2nd: SVD NIH, died at 5 months of age, no diagnosis
  - 3rd: CS, W&A
  - 4th: CS NIH, early NND
  - 5th: CS, W&A
- Referred with cystic hygroma at 13 weeks, hydrops and large kidneys
- CVS done, sample sent for NIH research
- TOP performed

- Seen again in 2015
- G7P5+1, living 2
- Still no results
- Massive hydrops, short long bones
- Cordocentesis performed, samples sent for NIH study and DNA banking

Sent back to local hospital, died at 4 months of age
Case 3: 750707

• Results: available in March 2017:
  • 6th pregnancy: mutation in FCRL4 gene splice site mutation, fetus is homozygous, both parents are heterozygous
  • 7th pregnancy: mutation in SLCI7A5 gene (Infantile Sialic Acid Storage Disorder), splice site mutation, fetus is homozygous, both parents are heterozygous

• 2 different genetic diseases both presenting with hydrops!!
Case 4: 5212512

- 4 NND with possible congenital disorder of glycosylation (CDG), and one previous anencephaly. No samples from index case and no previous genetic testing
- Presented at 8 weeks desperate for diagnosis
- After discussion: *duo exome from parents to start*, followed by prenatal sample to complete trio exome- save time!
- Results: positive mutation HADHB:NM_000183:exon9:c.631-1G>A
- Pathogenic variant causing severe and early lethal mitochondrial disease
- Current fetus heterozygous
Prenatal Genetic Testing at KFSH&RC: Impact on Pregnancy Outcome and Hospital Resources

- Disease/Gene/Mutation previously identified in the family
- Mother is pregnant
- Targeted genetic test on fetus
- Report issued in TAT of 2 weeks

Number of Prenatal Genetic Tests Performed by MFM 2011-2016

Overall Reporting Results 2011-2016
(Over 1350 total tests in over 200 genes in 150 diseases)

Approximately 350 affected fetuses reported

- 2011: 129
- 2012: 149
- 2013: 203
- 2014: 219
- 2015: 257
- 2016: 388

- WILDTYPE NORMAL: 28%
- CARRIER: 23%
- AFFECTED: 47%
- REDRAW: 2%
Impact on the Health Services

A family with SMA:
2 previous affected children: each survived for 20 days in NICU, ventilated
Minimal cost per child: $20 \times SR\ 7000 = SR\ 140,000$

If prenatal diagnosis is done: $\frac{1}{4}$ chances of abnormal fetus
Cost per test: $SR\ 3500 + \text{cost of procedure} = SR\ 6000$
Maximal cost to diagnose one case: $SR\ 24,000$
Additional cost for admission/ TOP: $SR\ 6,000$

Total cost of prenatal testing: $SR\ 30,000$----$20\%\ of\ the\ cost$
Our Services

- We accept referrals from all around the country and neighboring countries.
- We arrange urgent appointment as needed through our coordinators
- We are a phone call away- personal communication is the best
What is a MATERNAL-FETAL MEDICINE (MFM) subspecialist?
A physician who has advanced knowledge and training in medical, surgical, obstetrical, fetal, and genetic complications of pregnancy & their effects on both the woman and fetus.

**MFM Subspecialists provide**
1. **consultations**
2. **co-management**
3. **transfer of care**

for women with complex conditions before, during, and after pregnancy.

**MFM Subspecialists provide peer and patient education:**
AND

**MFM subspecialists work with ALL OBSTETRIC PROVIDERS**
including physician assistants, nurses, NPs, CNMs/CMs, family physicians, and obstetric-gynecologists to manage HIGH-RISK PREGNANCIES.

What is a HIGH-RISK PREGNANCY?
One that threatens the health or life of the woman or her fetus.

- **SICK WOMEN get pregnant**
- **PREGNANT WOMEN get sick**

**EXISTING CONDITIONS**, such as high blood pressure, obesity, diabetes, or being HIV-positive

- Rates of Gestational Diabetes (GDM) and pre-GDM have DOUBLED in the last 14 years.
- Over the last 30 years, first trimester use of prescription medications has increased by more than 50%.

- 60% of women of reproductive age are obese or overweight.

**MULTIPLE GESTATION**
In 2014 3.3% of all babies born were TWINS, TRIPLET OR HIGHER-ORDER MULTIPLES accounting for almost 140,000 births in the U.S.

- The number of MULTIPLES Born in The U.S. is at an ALL-TIME HIGH, according to the National Center for Health Statistics.

**PROBLEMS with THE FETUS**
Birth defects affect one in every 33 babies born in the U.S. each year.

- Birth defects are the leading cause of infant deaths, accounting for 20% of all infant deaths.

**COMPLICATIONS from PREVIOUS PREGNANCIES**
e.g., preterm birth, preeclampsia, IUGR

Society for Maternal-Fetal Medicine
High-risk pregnancy experts