Company information

2008.
Profile

The main profile of FML’s activity is to provide effective support for healthcare organizations on the field of prenatal diagnostics. With co-operation with the parent company FML is the market leader in biochemical prenatal screening of Down’s syndrome (and other prenatal abnormalities) in Hungary.

FML provides complex logistic system, clinical laboratory and reporting service all over Hungary.
Laborexpert Ltd. (parent company) was established in 1991. The main activity was distribution of immunchemical reagents (tumour markers, endocrinology, emergency tests) and analyzers to clinical laboratory.

Since 2002 we took part in establishment of biochemical screening of Down disease and other chromosome number disorders using maternal sera in 8 centres in Hungary. Two methods are applied in routine: (1) the **combined test** during the early period of pregnancy (11-13 week, free-βhCG and PAPP-A – completing it with US measurement of nuchal translucency) and (2) **triple test** (15-18 week, AFP, hCG and unconjugated Estriol). We prepared the Hungarian version of a risk-evaluating software (PRISCA software) and we sponsored to edit informative brochures of biochemical screening for parents. We participate in numerous domestic meetings concerning this topic and sponsored participation of professionals, publications, and we also organized scientific meetings concerning chromosome number disorders.
History in our days

Event of great significance was in history of Laborexpert Ltd. when the company was establish its subsidiary, Fetal Medicine Laboratory Ltd. (FML) in 2007. This time was enormous breakthrough in biochemical screening of Down’s syndrome in Hungary.

The mission of FML that gives chance all pregnancy to take part in screening anywhere in the country. So we provide complex logistic system, clinical laboratory and reporting service all over Hungary.

All of activities of FML is certified by TÜV Reinland Intercert for EN ISO 9001:2000 qualification.

The laboratory participates in the United Kingdom National External Quality Assessment Service (UKNEQAS) scheme for First Trimester Down’s Syndrome Screening and Second Trimester Down’s Syndrome Screening as well.

There are many different screening tests available and we can provide all of them: double, combined, triple, quadruple, serum integrated, integrated tests.

Co-operate with clinics, hospitals and private health centers we were performed more than 90,000 screenings in Hungary.
References of FML in Hungary

- **Semmelweis University**, 1st Department of Obstetrics and Gynecology (Genetic Centrum) – Budapest
- **University of Szeged**, Department of Obstetrics and Gynecology (Genetic Centrum) – Szeged
- **University of Pécs**, Department of Obstetrics and Gynecology (Genetic Centrum) – Pécs
- **Petz Aladár County Hospital**, Department of Obstetrics and Gynecology (Genetic Centrum) – Győr
- **Zala County Hospital** (Genetic Centrum) – Zalaegerszeg
- Tolna County Balassa János Hospital – Szekszárd
- Komárom-Esztergom County St. Borbála Hospital, Tatabánya
- Hospital of Baja, Baja
- Margit Hospital, Csorna
- Erzsébet Hospital, Sopron
- Karolina Hospital, Mosonmagyaróvár
- Selye János Hospital, Komárom
- St. Pantaleon Hospital, Dunaújváros
Aim of Down’s syndrome screening

The goal of maternal serum screening is to determinate the group of pregnant women whose baby has a higher risk for Down’s syndrome.

It gives informations about likelihood that baby has Down’s syndrome and it is not diagnosis.

It is very important that all pregnant women should join to one biochemical Down’s screening test.
Down’s syndrome

Down’s syndrome is a genetic disorder which causes delays in physical and intellectual development. Individuals with Down’s syndrome have extra chromosome 21 (Trisomy 21). It is the most frequently occurring chromosomal disorder. It occurs in approximately one in every 700 live births.

Some common physical signs:
• Flat face with an upward slant to the eye, short neck, and abnormally shaped ears
• Deep crease in the palm of the hand
• White spots on the iris of the eye
• Poor muscle tone, loose ligaments
• Small hands and feet

There are a variety of other health conditions that are often seen in people who have Down syndrome, including:
• Congenital heart disease
• Hearing problems
• Intestinal problems, such as blocked small bowel or esophagus
• Celiac disease
• Eye problems, such as cataracts
• Thyroid dysfunctions
• Skeletal problems
• Dementia—similar to Alzheimer’s
Down’s syndrome screening

In our days there are only invasive tests to diagnose Down’s syndrome (amniocentesis or chorionic villus sampling (CVS)). But the problem with them is that they can cause a miscarriage (1-2%).

Maternal serum screening provides information about likelihood that baby has Down’s syndrome by combining the information of non-invasive procedures:

- The findings from an ultrasound scan at 11-13+6 weeks (the nuchal translucency scan)
- Information obtained from the levels of some biochemical parameter in the mother’s blood.

The platform of determination of risk is maternal age.
Screening tests in 1st trimester

1. **Combined test** (nuchal translucency (NT) ultrasound scan plus blood test for free βhCG and PAPP-A)

2. **Double test** (only biochemical test including free βhCG and PAPP-A)

Amendment:

- **Human chorionic gonadotropin** hormone is produced by the placenta, and is used to test for the presence of pregnancy. A specific smaller part of the hormone, called the **beta subunit**, is increased in Down syndrome pregnancies.

- **PAPP-A**, which stands for pregnancy-associated plasma protein A, is produced by the covering of the newly fertilized egg. In the first trimester, low levels of this protein are seen in Down syndrome pregnancies.
Screening tests in 2nd trimester

1. **Triple test**: measures three markers - ßhCG, uE3 and AFP

2. **Quadruple test**: measures four markers - ßhCG, AFP, uE3 and inhibin A.

Amendment:

- **Alpha-fetoprotein** is made in the part of the womb called the yolk sac and in the fetal liver, and some amount of AFP gets into the mother's blood. In neural tube defects, the skin of the fetus is not intact and so larger amounts of AFP is measured in the mother's blood. In Down syndrome, the AFP is decreased in the mother's blood, presumably because the yolk sac and fetus are smaller than usual.

- **Estriol** is a hormone produced by the placenta, using ingredients made by the fetal liver and adrenal gland. Estriol is decreased in the Down syndrome pregnancy. This test may not be included in all screens, depending on the laboratory.

- **Human chorionic gonadotropin** hormone is produced by the placenta, and is used to test for the presence of pregnancy. A specific smaller part of the hormone, called the **beta subunit**, is increased in Down syndrome pregnancies.

- **Inhibin A** is a protein secreted by the ovary, and is designed to inhibit the production of the hormone FSH by the pituitary gland. The level of inhibin A is increased in the blood of mothers of fetuses with Down syndrome.
Integrated test: Combination of 1st and 2nd trimester screenings

1. **Serum integrated test:** combination of a blood test for PAPP-A at 1st trimester of pregnancy with a further blood test for AFP, uE3, βhCG and inhibin A at 2nd trimester of pregnancy

2. **Integrated test:** combination of nuchal translucency scan (NT) and blood test for PAPP-A at 1st trimester of pregnancy with a further blood test for AFP, uE3, βhCG and inhibin A at 2nd trimester of pregnancy
<table>
<thead>
<tr>
<th>Screening test (all include maternal age)</th>
<th>Cut off</th>
<th>DR</th>
<th>FPR</th>
<th>OAPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test dublu</td>
<td>1:250</td>
<td>77 %</td>
<td>7,1 %</td>
<td>1:44</td>
</tr>
<tr>
<td>Triple test</td>
<td>1:250</td>
<td>81 %</td>
<td>6,9 %</td>
<td>1:38</td>
</tr>
<tr>
<td>Quadrruple test</td>
<td>1:250</td>
<td>84 %</td>
<td>5,7 %</td>
<td>1:30</td>
</tr>
<tr>
<td>Combined test</td>
<td>1:250</td>
<td>83 %</td>
<td>4,7 %</td>
<td>1:25</td>
</tr>
<tr>
<td>Serum integrated test</td>
<td>1:150</td>
<td>81 %</td>
<td>3,2 %</td>
<td>1:17</td>
</tr>
<tr>
<td>Integrated test</td>
<td>1:150</td>
<td>87 %</td>
<td>1,9 %</td>
<td>1:10</td>
</tr>
</tbody>
</table>

(N.J.Wald et al.: First and second trimester antenatal screening for Down’s syndrome: the results of the SURUSS, J. Med Screen 2003; 10; 56-104, Table 30.)

**DR** - Detection rate, the proportion of affected pregnancies with positive screening results

**FPR** - False-positive rate, the proportion of unaffected pregnancies with positive screening risk

**OAPR** - Odds of being affected given a positive results
FML has an own developed informatics-system which is specialized to manage Down’s screening, named **FML Global Network**.

This system could keep in touch with all screening centers, logistic centers, laboratories and it communicates with the risk calculation program.

**Promoted processes:**
- Data recording: Partners registered patient data and information about blood collection and sample handing
- Checking function in logistic center
- Result manager function
- Interface with risk calculation software (Alpha)
- Validation function
- Reporting function
FML Global system

- **On-line** communication between Screening centers, Logistic Centers and Laboratories.
- Data transmission: HTTP protocol encrypted, VPN connection
- **Interface** chance with host informatics system
- Automatic **form generation** (sending form, consent)
- **Barcode** generation (sample follow up)
- User specific images
- Different **authority** levels
- Checking, finding, filter function
- Automatic on-line **bracing**
Sample collection

- Human serum should be used. No additives or preservatives are required to maintain integrity of the sample.
- Blood should be collected aseptically by venipuncture.
- Centrifuge not later than 30 minutes after drawing.
- After centrifuge make 3 aliquots in plastic tubes. The minimum volume of the aliquot is 1000 µL.
- Close all tubes with color stopper. (The color of stopper provides information about intended use.)
- Freeze all tubes immediately. Avoid repeated freezing and thawing cycles.
Logistics

Fetal Medicine Laboratory has close schedule to transport freezing sample from partners to logistic center. Colleagues of FML collected samples every week in the same time from all partners. FML provides special boxes to freezing transport, that guarantee the adequate temperature all seasons. FML controls the temperature of samples from freezing through transport till to arriving.
Measuring in laboratory

In the laboratory of FML up-to-date automatized immunoassay tests are used to determinate biochemical markers of Down’s syndrome: AFP, free-βhCG, βhCG, unconjugated Estriol, PAPP-A and Inhibin-A.

All the tests are optimized to determinate markers in pregnant population and they are CE marked.

The laboratory determinations are performed according to the international regulations.
Risk calculation

FML protocol is in compliance with the Wolfson Institute of Preventive Medicine (UK) guidelines for risk calculation. Risk is calculated with Alpha software (Logical Medical System, London) and FML Global Network provide the possibility to produce user specific patient reports.

Our recommendation for screening centers without good practise in ultrasound: double, quadruple and serum integrated test.

Our recommendation for screening centers with good practise in ultrasound: combined, quadruple and integrated test.
Alpha
the risk calculation software

Alpha is the leading interpretive software for use in antenatal screening for Down's syndrome and open neural tube defects (NTDs). It was launched in 1988, and remains the standard against which most others are compared. It is based on published scientific data, and under the supervision of Professor Nicholas Wald is regularly updated in the light of new scientific advances. Over 9 million women in 49 countries have been screened using alpha.

• Alpha uses a woman’s age, the levels of screening markers, and other information about the pregnancy, to estimate the woman’s risk of having a pregnancy with Down's syndrome or an NTD. The risk of trisomy 18 (Edward's syndrome) and Smith-Lemli-Optiz syndrome (SLOS) can also be printed, if they are high.

• Alpha is suitable for
  – First trimester screening for Down's syndrome using nuchal translucency and biochemical markers
  – Second trimester screening for Down's syndrome and NTDs using biochemical markers
  – Integrated screening for Down’s syndrome, using first and second trimester markers to provide a single estimate of risk

Alpha now carries a CE mark, in accordance with the requirements of the European Directive on in-vitro medical devices (Directive 98/79/EC) and the UK Medical Device Regulations 2002:618.
Principle of risk calculation

Based on maternal age

Factors affecting:
- Insulin dependent diabetes
- Smoking
- Maternal weight
- Ethnic group
- IVF pregnancy

Excluding criteria:
- Twins
- Vaginal bleeding in last 7 days
- Amniocentesis or chorionic villus sampling before sampling
Quality control

FML is certified by TÜV Reinland for EN ISO 9001:2000 qualification.
FML’s screening protocol is in compliance with the Wolfson Institute of Preventive Medicine (UK) guidelines.
Biochemical tests are performed by up-to-date automatized CE marked immunoassay tests which are optimized for pregnant population.
The laboratory participates in the United Kingdom National External Quality Assessment Service (UKNEQAS) scheme for First Trimester Down’s Syndrome Screening and Second Trimester Down’s Syndrome Screening as well.
Summary

FML is the market leader company on the field of Down’s syndrome screening in Hungary.

We provide full Down’s screening service for any health organization to become a qualified Down’s screening center, including:

- Screening protocol
- Full quality control system
- Logistic system
- Laboratory background
- Risk assessment and reporting
- FML Global Network on-line information system
- Regular education for professionals
- Continual professional support
- Marketing, advertising support