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Lactate Level in Amniotic Fluid, a New Diagnostic Tool

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1. Introduction

If exhaustion or muscle fatigue is discussed in a general conversation, usually people will refer lactate accumulation as a primary cause. Lactate accumulates in blood and tissues during exercise, particularly when oxygen is lacking. The concentration is highest at or just following exhaustion. Lactate has historically been considered as a dead-end waste product of anaerobic metabolism due to hypoxia and the primary cause of fatigue (Berzelius 1808; Araki 1891; Hartree & Hill 1921; Hill 1922). Lactate has also been considered as a key factor in acidosis-induced tissue damage; however the role of lactate in metabolism has changed during the last decade (Brooks 1986; Brooks 2002; Brooks 2002) Lactate is no longer considered as a harmful end-product, but mainly one of the central players in cellular and whole body metabolism.

The breakdown of glycogen during anaerobic conditions leads to intracellular accumulation lactic acid. Lactic acid is a strong monocarboxylic acid (Pka 3, 86) and it dissociates easily at physiological pH into lactate and hydrogen ions (H+). The lactate itself has been considered to have little effect on muscle contractions. However, increased production of H+ and reduced pH with acidosis has classically been considered as the cause of muscle fatigue. The role of reduced pH as an important cause of fatigue has been challenged (Karlsson et al. 1975). Present day knowledge is that anaerobic metabolism with the production of lactic acid might also lead to increased production of other factors, like phosphate (Allen et al. 2002; Westerblad & Allen 2002; Westerblad et al. 2002) which is likely to have a more prominent role in muscle fatigue.

One important finding, which has influenced the hypotheses for this thesis, is that the myometrium is a lactate producer (Taggart & Wray 1993; Taggart et al. 1996; Taggart et al. 1997; Taggart & Wray 1998; Wray et al. 2003; Quenby et al. 2004), and the level will increase when there is a lack of oxygen.

The essential function of amniotic fluid (AF) is to cushion the fetus. The fluid gives the fetus space to grow, and allows it to undergo a `physical´ development. The AF function is also to protect the fetus from trauma and to maintain temperature. It also has a minimal nutritive function.

2. Energy metabolism

The main substrate for energy metabolism is glucose (Meyer 1920). Under normal conditions, with sufficient oxygen supply, aerobic metabolism occurs. Here glucose is broken down along the glycolytic pathway, and the resulting pyruvate enters the citric acid cycle (Fig.1). Energy is produced along the glycolytic pathway, together with carbon dioxide (CO_2) and water (H_2O). Nicotinamide adenine dinucleotid (NAD+) is a powerful hydrogen ion acceptor. In the citric acid cycle NAD+ accepts an H+ to produce NADH. In the reaction O_2 is consumed, and a large amount of energy is released (36 ATP).
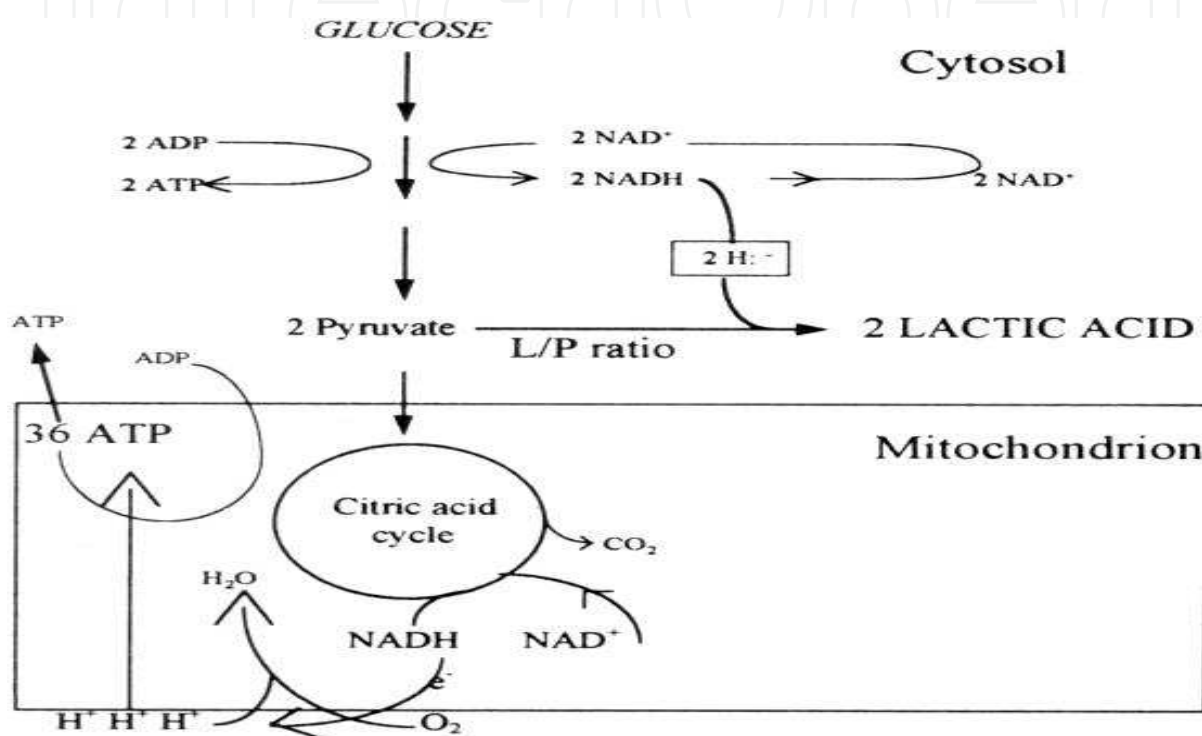

Fig. 1. From: Intrapartum Fetal Hypoxia and Biochemical Markers; a review (Nordstrom & Arulkumaran 1998).

If oxygen supply reaches a critical low level, the metabolism will change to become anaerobic. Here, instead of entering the citric acid cycle, pyruvate is reduced to lactic acid and H+. This reaction is catalyzed by the enzyme lactate- dehydrogenase (LDH), and also involves the oxidation of NADH to NAD+. NADH is generated in glycolysis, and re-oxidised into NAD+. Under anaerobic conditions, this oxidation is impaired, resulting in accumulation of NADH, promoting the conversion of pyruvate to lactate.

In normal conditions there is a steady state relation between lactic acid/pyruvate (L/P). If oxygen supply is limited, a progressive lactate acidemia (metabolic acidosis) develops. Anaerobic metabolism produces less energy (2 ATP/glucose) compared with aerobic conditions (36 ATP/glucose).

2.1 Cellular energy production

With prolonged lack of energy due to anaerobic metabolism, there is difficulty in maintaining cellular integrity. Cellular functions rely on ion gradients across cell

membranes. Ion pumps require ATP to function. Regeneration of sufficient amount of ATP can no longer be sustained if anaerobic metabolism continues. In this catabolic situation, the basic cellular functions start to fail. Three different cellular energy statuses are described (Nordstrom & Arulkumaran 1998). The first one is aerobic when there is sufficient amount of oxygen and a lot of energy is produced in the form of ATP. This is an efficient way of energy production. The two others are dependent on the level of oxygen supply, and if the situation is compensated or not. Lack of oxygen forces the cell into an anaerobic metabolism with production of lactate and H+. Energy is produced but to a limited amount. If the demand of energy is still sufficient, the cellular energy status is compensated. This can continue as long as energy demand and production is in balance. If the situation is progressing, regeneration of ATP can no longer be keep up with demands and the cellular energy status will be decompensated

2.2 Buffering systems

In a normal state, the buffering systems of the organism have the capacity to maintain pH within a physiological range. It is important for the organism to maintain stability in pH, i.e. H+ concentrations. A fluctuation of H+ is dangerous for the cell. If the concentration of H+ rises it may disturb cellular function and affect the activity of cellular enzymes.

There are different buffering systems within the organism. The two most important systems are the bicarbonate and the protein buffering systems. These two systems main functions are to neutralize H+ which has been produced through anaerobic metabolism. The role of the bicarbonate buffer is to establish equilibrium between CO2, H2CO3, bicarbonate (HCO3) and hydrogen ions (H+), via the equation shown below (Siggaard-Andersen 1971).

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO3^-$$

In this reaction CO2 is passing through and at the end is converted to bicarbonate, which leaves the red blood cells by means of an exchange of chlorides. The equation goes from left to right and back again several times until a steady state condition is established. At steady state total cellular CO2 production equals CO2 elimination.

3. Lactate

Knowledge about lactate is a rapidly changing field, and our understanding of the role of lactate metabolism has changed dramatically from the classical views held in the 19th century. The lactic acid era began in 1808 when Berzelius at the Karolinska Institute in Stockholm, discovered elevated concentrations of lactate in `the muscles of hunted stags´ (Berzelius 1808). Araki showed in 1891 that lactic acid concentration in exhausted animal muscles was proportional to the amount of exercise and was associated to O2 availability (Araki 1891). Some 100 years after Berzelius, Fletcher and Hopkins showed that lactic acid appeared in response to muscle contraction in human muscle (Fletcher & Hopkins 1907).They also showed that accumulated lactate disappeared when oxygen became available. Later on the `lactic-acid-cycle´ was described, and showed two distinct pathways in metabolism, the aerobic and the anaerobic. The coming period was called `the revolution in muscle physiology´. From the 1930's to the early

1970′s lactic acid was largely considered to be a `dead-end metabolite of glycolysis after muscle hypoxia´ (Meyerhof 1920; Hill 1922). Lactic acid was also believed to be the major cause of muscle fatigue. Since the early 1970′s, a `lactate revolution´ has occurred (Hermansen 1981; Wasserman 1984). At present we are in the midst of a `lactate shuttle era´ with the introduction of the `lactate shuttle hypothesis´ (Brooks GA.1986; Brooks 2000; Brooks 2002).

3.1 Muscle fatigue

It is well known that muscle performance may decline with prolonged or intense muscle activity, especially if there is a shortage of 02 (Allen et al. 1995; Westerblad et al. 2002). This decline is known as muscle fatigue. The causes of fatigue are probably multiple, but the consequence is that the power output may be drastically reduced. The consequence of lost power is obvious during sporting activity, for example, in endurance sports. It is almost impossible to maintain a marathon race if the muscles are exhausted. When a muscle goes from rest to high-intensity exercise a marked acidification occurs because of the shortage of 02. The energy demand exceeds the capacity from available aerobic metabolism. The metabolism will enter the anaerobic pathway and the ATP required will come from anaerobic metabolism. Anaerobic breakdown of glycogen leads to intracellular accumulation of inorganic acids such as, for example, lactic acid. Lactic acid is a strong acid and dissociates easily to lactate and H+ at physiological temperature. Lactate might therefore have limited effect of its own on the muscle contractions. The traditional thinking was that H+ is produced together with lactate, and H+ created the pH change and was the important cause of fatigue.

Recently presented data provide substantial support for that increased inorganic phosphate (Pi) having a key role in muscle fatigue (Westerblad et al. 1991; Westerblad et al. 1998; Westerblad 2002; Westerblad & Allen 2003), especially at physiological temperature (Westerblad et al 1997). For acidosis, on the other hand, most recent data indicate that its depressive effect on muscle contraction is limited. Other studies express doubts about the effect of Pi, and indicate that it is too early to dismiss H+ as an important factor in muscle fatigue (Fitts 2003).

The way in which human uterine smooth muscle cells metabolize and meet the energy demands during labor is still obscure. Energy is produced by glycolysis, ending with the formation of ATP and pyruvate. It has in different studies been demonstrated that the human uterus utilizes glucose as its main energy substrate at term pregnancy. It seems that smooth muscle cells in uterus are capable of producing lactate at a higher rate under aerobic conditions compared with striated muscle cells.

Fatigue has many sources that may be present in different sites in the muscle cells (Taggart & Wray 1998). Many constituents of muscle metabolism change during fatigue and for each of these metabolites we need to know which role they have in the regulation of the muscle contraction. Despite nearly 200 years of muscle function research, the question of muscle fatigue still remains partly unresolved.

3.2 Lactate shuttles

Earlier, lactate was considered to be transported across the membrane only via passive diffusion, depending on a pH gradient, (Crone 1963; Brooks 2002; Philp et al. 2005). Subsequent publications revealed a carrier-mediated transport of lactate across membranes.

An entire family of monocarboxylate transport proteins (MCT), which facilitate the transport of lactate in and out of the cells, has been described (Bonen et al. 1997; Brooks et al. 1999; Bonen 2000; Bonen 2001). During exercise lactate and H+ move in and out of tissue primarily via MCT1 and MCT4, diffusion of undissociated lactate constitutes a smaller component of the transport. It has been proposed that the force of smooth muscle contractions during labor is reduced by hypoxia in uterus, and studies have pointed out that myometrial lactic acidosis is associated with dysfunctional labors.

Lactate exchange is a dynamic process with simultaneous uptake and release between cells at rest and during exercise. At rest muscles slowly release lactate in to the surrounding fluids on a net basis, but cells may also show a small net uptake. During exercise, muscle tissue produces lactate rapidly. This results in an increased intracellular concentration of lactate and an increased net output of lactate from the muscle cells to the surrounding fluids. During recovery there is a net uptake of lactate from the ambient fluid by resting muscles, or other muscles that are exercising at low or moderate intensity. During prolonged exercise of low to moderate intensity, the muscles that originally released lactate on a net basis at the onset of exercise may actually reverse it to net lactate uptake. The conclusion from many recent studies is that lactate is a useful metabolic intermediate which can be exchanged rapidly between tissue compartments (Brooks 2002). Lactate can also be used as a substrate in aerobic condition.

4. The uterus

The uterine muscle has a dualistic function. It has to shelter the growing fetus during pregnancy within the uterine cavity. To fulfil the demand of pregnancy/parturition the human uterus has a unique construction. The uterine cavity is surrounded by smooth muscle where the myocytes are arranged in bundles embedded in connective tissue. This arrangement gives uterus elastic properties and facilitates the transmission of contractile forces generated by individual muscle cells. The uterine muscle has a relatively relaxed state during pregnancy. Second, when labor starts the uterus becomes a strongly coordinated working muscle with a high level of activity.

Blood supply of the uterus is provided by the uterine and ovarian artery. The arteries meet on the surface of the uterus where they are connected. From this connection leaves the radial artery that penetrates the myometrium and supplies both the myometrium and the placenta during pregnancy and labor. During pregnancy the myocytes undergo hypertrophy and hyperplasia resulting in significant size and volume growth of the uterus and increased demand for adequate circulation.

In the last part of pregnancy the uterus in preparation for labor through changes in the ion and hormone balance to optimize the conditions for effective synchronized contractions. The number of gap junctions and calcium concentration in the uterine tissue increases. The relaxing NO decreases. Oxytocin and prostaglandins have an important stimulating role. Oxytocin contributes via oxytocin receptors to increased contractility of the myocytes. Earlier studies of contractile myometrial activity are mostly concerned with the hormonal control. We have knowledge about the effect of oxytocin (Rezapour et al. 1996), gestagens and estrogens (Roy & Arulkumaran 1991; Spencer et al. 2005), as well as the prostaglandins during labor (Challis 1974). Their ultimate effects are assumed to be modified by local factors in the tissue,

e.g. metabolites. Extended knowledge about these metabolites seems to be of importance, especially in the light of the clinical expression of labor dystocia (Steingrimsdottir et al. 1995).

During the late 1980's and the 1990's several studies have been published on myometrial activity (Wedenberg et al. 1990; Wedenberg et al. 1991; Ronquist et al. 1993; Steingrimsdottir et al. 1995; Wedenberg et al. 1995). They have shown that the pregnant myometrium has a low energy charge (EC), described as an index of energy status, and compared with striated and cardiac muscles. The difference was considered to be due to the very special demand of the uterine muscle, compared to other muscles. The cardiac muscle has to work continuously, with only short periods of rest (diastole). Striated muscles must work instantly on command. The uterine muscle remains relaxed for long periods of time and then, only for short periods (labor), has to be transferred to a state in which strong contractions are required. This situation demand energy (Steingrimsdottir et al. 1993; Steingrimsdottir et al. 1995; Steingrimsdottir et al. 1997; Steingrimsdottir et al. 1999). Studies have shown an increased content of glucose in the pregnant smooth muscle in term pregnancy, compared with early pregnancy and the non- pregnant uterus. This finding along with a positive artriovenous difference in blood-glucose across the uterus (i.e. net uptake), indicates glucose to be the principal nutritive metabolite for the pregnant uterine muscle (Steingrimsdottir et al. 1999).

The anaerobic pathway seems to be more active in the myometrium than in striated muscles. The Lactate/Pyruvate ratio, an indicator of anaerobic metabolism, is reported to be higher in the pregnant myometrium compared with other muscles (Steingrimsdottir et al. 1995). The lactate content of pregnant uterine muscle has been reported to be doubled compare with the skeletal muscle, probably reflecting a vigorous glycolytic flow when the uterus is active.

The uterus undergoes a general metabolic preparation for a hypoxic condition in late gestation. A significant physiological alkalinisation of the muscle over the last few weeks of pregnancy has been shown (Parratt et al. 1995). This might therefore contribute to the mechanisms ensuring that strong and efficient contractions occur during labor, when acidity is added during normal myometrial contractions.

A number of papers have been published on myometrial acid-base balance, and correlation to inefficient contractions and dysfunctional labor. One finding is that acidification of the myometrium with accumulation of lactate, and a decrease of myometrial pH during contractions, could depress uterine contractions and thereby contribute to dysfunctional labor. It has been shown that lactate concentration of myometrial capillary blood is significantly higher in women having a caesarean delivery due to dystocia than in women having an elective caesarean section or being operatively delivered with normal contractions. Furthermore, reduced pH and raised lactate concentrations in myometrial strips change regular contractions to irregular ones with reduced amplitude in vitro studies. One of the suggested clinical explanations for this process was that during labor blood vessel supply might be occluded while the uterus is contracting. The irregular contractile pattern in dysfunctional labor might lead to extended occlusion of the uterine vessels. Extended occlusion might lead to a lowering of the myometrial oxygen levels and accumulation of lactic acid. Thus, despite the inefficient contractions, there is an inadequate reoxygenation of the uterus. There is a suggestion that that there is a variation in response to intermittent hypoxia in different women. The recovery period from the low oxygen episode after occlusion might differ.

The knowledge that amniotic fluid (AF) contains high concentration of lactate has been published for the first time in the 1970's. Some publications have suggested that the source of lactate in AF is the fetus itself, mainly through urine and lung excretion. Several reports have suggested the myometrium as the most important lactate producer. The lactate concentration in amniotic fluid is reported to be 4 - 6 times higher as compared with fetal and maternal blood. However, from the literature it is not clear from where the high AF lactate concentration is derived.

5. Labor

"*In Africa the sun should never rise twice during labor, then it's dangerous*", an Old African saying was recounted by an African obstetrician at `Federation International Gynecologie Obstetrique´ (FIGO) 2006.

5.1 Normal delivery

Normal childbirth is a retrospective diagnosis that refers to spontaneous delivery starting after a full-term pregnancy, with absence of risk factors and/or complications. The goal of all deliveries is healthy mother, healthy baby and a positive childbirth experience.

In the first stage of labor, uterine contractions increase in frequency and strength. Since Freedman's work in the 1950s, it is considered that normal cervical dilatation during the first stage of labor is 1 cm/hour which gives a mean duration of first stage of 4.5 hours. An opening stage with a 2-3 hours delay is considered as extended or dystosic (Friedman 1955).

5.2 Labor dystocia

Labor dystocia is a common worldwide obstetrical problem, and is one of the main indications for operative intervention during parturition. Labor dystocia is clinically defined as slow/arrest of progress during labor, i.e. cervical dilatation and descent of the presenting part. It is estimated that labor dystocia occurs in about 20% of all deliveries worldwide. However, it is difficult to find a precise definition of the diagnosis of dystocia. The usual method to identifying labor dystocia is to use a partogram with an `alert line´ representing cervical dilation of 1 cm per hour and an `action line´ drawn 2-4 hours to the right of the `alert line´ (Philpot 1972). The clinical method of identifying dystocia is when the graphically plotted rate of progress crosses the action line or if no progress is made over the previous 2 hours (Lavender 2008).

Labor dystocia is associated with increased risks, such as labor abnormalities, increased risk of instrumental/operative intervention, depressed Apgar score at 5´minutes and extended need for newborn care. Dysfunctional labor is also associated with a higher frequency of postpartum infections, higher estimated maternal blood loss and lengthened maternal and newborn hospital stay.

5.3 Partogram

According to World Health Organisation (WHO) every delivery in the world should have a partogram presented during labor (Kwast et al 1994). The partogram detects maternal and fetal complications and the progress of labor. The background of the partogram, the cervicoplot, was constructed by Friedman during the 1950´s. Friedman analyzed the average

of cervical dilatation speed during active phase of the 10% women with the slowest labor progress, and estimated a normal progress to be 1 cm /hour. Original curves of the cervical dilation were sigmoid with a clear transition between first and second stage of labor. The partogram has been an important tool in obstetric care since the 1950's.

Some years after Friedman's published work, Philpot and Castle constructed the first partogram. The sigmoid curve was now translated to a straight line with an expected progress of labor with 1 cm/h. This line, which is plotted in most partogram of today, is called the alert line (AL) and corresponds to the expected labor progress. The midwife or the obstetrician in charge should pay attention if labor progress deviate from the expected progress. In the development of the partogram, AL was supplemented with Action Line (ACL). When progress of labor passed ACL a dysfunctional labor was diagnosed. If labor progress crossed the ACL, intervention is recommended primarily with amniotomy and thereafter with oxytocin stimulation. The location of the ACL differs between countries and is usually placed 2-4 hours from the AL. In Sweden the ACL with the 2-hours shift is used.
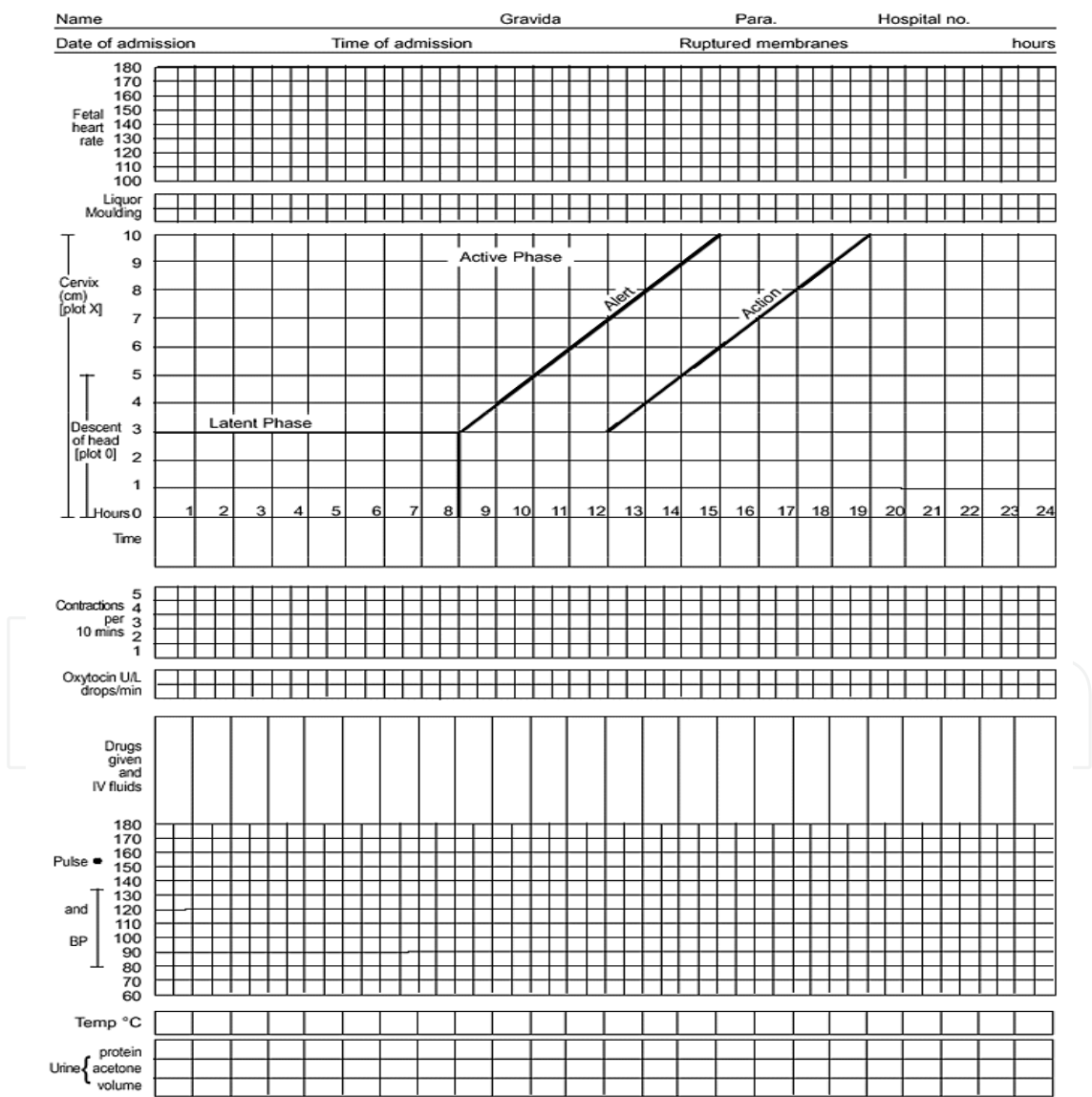

Fig. 2. The WHO Partogram

In early 1990's the WHO partogram was evaluated in a review and it was found that the use of partogram reduces the proportion of deliveries with dystocia, the number of emergency caesarean section and the frequency of stillbirths. Against this background, WHO has recommended an universal use of the partogram since 1994 (Kwast et al 1994).

Nowadays the partogram has been questioned, particularly in terms of design and efficiency. In a Cochrane review the use of partogram was evaluated and a compare with no use of partogram. An evaluation of the partogram with different placement of the ACL was also made. The results were inconclusive and showed that the use of partogram neither decreased the caesarean rates nor gave higher Apgar score at 5 minutes. Four hours displaced ACL lowered the proportion of deliveries stimulated with oxytocin. ACL with 2-hour shift seemed to provide better maternal delivery experience, but no other benefits. In summary, design and use of the partogram is questioned and there is a need for other complementary methods to monitor delivery and to identify slow progress of labor.

5.4 Active management of labor

In the late 1960s 0´Driscoll and co-workers at National Maternity Hospital in Dublin, Ireland, carried out some pioneering work on normal/dysfunctional labor (O'Driscoll et al. 1969; O'Driscoll et al. 1973). They approached the management of labor in nulliparas' women, which is nowadays referred to as `active management of labour´. The method includes 1) strict criteria for the diagnosis of labor, 2) early rupture of the membranes, 3) prompt intervention with oxytocin and 4) a commitment to never leave the labouring women unattended during the period of labor. This constitutes `active management of labour´.

Trials have been conducted with some of the strict diagnostic criteria such as early amniotomy, early oxytocin stimulation in the event of abnormal progress of labor (inefficient myometrial contractions), and a commitment to never leave a labouring women unattended during the period of labor. Most of these studies have, however, been based on normal labor and not on dystosic ones. Some criticism has been made of the aggressive approach, and a combination of these interventions. There have only been a few randomised studies with `the total package of management of labor´ (Akoury et al 1988; Turner et al. 1988; Boylan et al 1991; Lopez-Zeno et al 1992; Frigoletto et al 1995), and only one of these showed significantly reduction in odds ratio (OR) for caesarean birth associated with active management (Lopez-Zeno et al 1992). In contrast continuous professional support in labor has been shown to reduce the rate of operative interventions.

6. Amniotic fluid

6.1 Amniotic fluid production

The essential function of AF is to cushion the fetus (Williams et al. 1980). The fluid gives the fetus space to grow, and allows it to undergo a `physical´ development. The AF function is also to protect the fetus from trauma and to maintain temperature. It also has a minimal nutritive function.

In the first half of pregnancy AF has a composition similar to fetal extra cellular fluid. The volume is closely related to fetal weight, and the skin of the fetus offers no resistant to movement of fluid. AF at this stage may be regarded as an extension of fetal extra cellular fluid. Beyond midpregnancy (about 20 weeks) the fetal skin keratinizes, and continuity between the fetal extra - cellular fluid and AF is lost. AF becomes completely external in the sense that it can now no longer equilibrate with either the fetus or the mother. After keratinisation of the fetal skin, the AF osmolarity decreases. A part of the changing composition reflects the increasing maturity of the fetal kidneys. The fetal kidneys begin to produce urine at about 12 weeks of gestation. Low osmolarity provides a large potential osmotic force for the outward flow of water across the intra- and transmembraneous pathways.

The regulatory mechanisms to achieve an adequate AF volume operate at three levels; placenta control of water and solution, transfer regulation of inflow and outflow by the fetus, and maternal effects of the fetal fluid balance. The most contributing proportion of the AF balance is the fetus and its urine production, and the AF ingested by the fetus through swallowing. A smaller contribution of AF is distributed by the fetal pulmonary fluid production, and fluid filtering through the placenta and the membranes.

The volume of amniotic fluid each week of gestation is quite variable. In healthy pregnancies the AF volume has its maximum at 32-34 weeks, averaging 800 ml. Thereafter it declines, and the decline will be most marked post term.
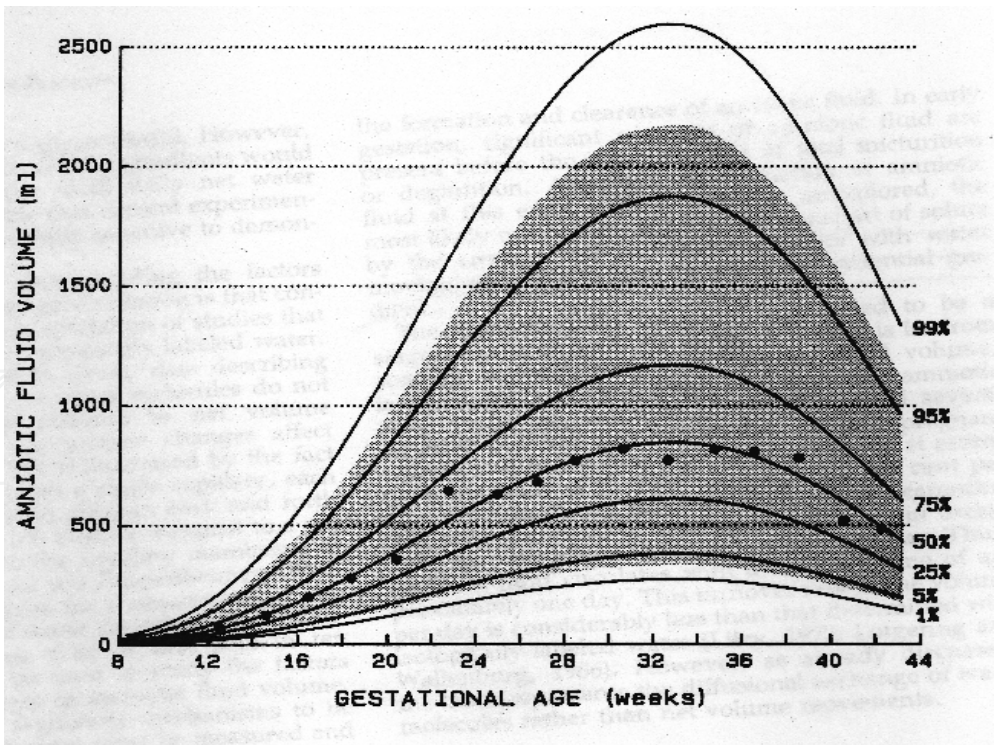

Fig. 3. AF volume as a function of gestational age. Dots represent measured volumes with 2 week intervals (mean) in 705 women. Shaded area represents 95% confidence interval. (From: William's Obstetrics 21st edition, 2001).

7. Lactate in AF, a new diagnostic tool in labor

No major improvement has occurred in the diagnostics of dysfunctional labor since the introduction of the "partogram" by Friedman and Philpot in the 1970´s. Dysfunctional labor is still one of the leading obstetrical problems, worldwide. About 20% of all deliveries have been shown to have an abnormal labor progress.

Dysfunctional labor is according to WHO defined as "a clinical deviation from expected progress" (no dilatation of cervix by 1 cm/hour, or no progress in 2 hours).The partogram is recommended to be used in all deliveries. Dysfunctional labor involves a long and painful delivery. The woman is in active labor, but the delivery progress ceases and the dilation of cervix does not proceed. The fetus does not pass through the birth canal, and the delivery comes to a halt. The reason behind dysfunctional labor is very little known, and several facts are probably due to a dysfunctional labor.

A prospective observational study was performed at Dept of Obstetrics and Gynaecology at South General Hospital, Stockholm, Sweden in 2002-2004 (Wiberg-Itzel et.al 2008). 75 women with a healthy and normal pregnancy and a spontaneous onset of labor were included in the study. AF was collected from an intrauterine pressure catheter and analyzed blinded every 30 minutes during the active phase of labor. The result was then related with the obstetrical outcome (spontaneous vaginal or operative delivery due to dysfunctional labor). The results showed that a high level of lactate in the amniotic fluid (>10.1mmol/l) at two consecutive measure during the active phase of delivery, had a strong association with the diagnosis of dystocia.

A second prospective observational study was carried out at the same hospital in Sweden between 2006-2008 (Wiberg-Itzel et. al 2010). AF from 850 healthy, normal deliveries was collected at every vaginal examination during labor. The samples were analyzed blinded. The purpose of this study was to evaluate if the level of lactate in amniotic fluid, together with the partogram recommended by the WHO could improve the diagnostics of an arrested labor. The study showed that the combination of the level of lactate in amniotic fluid and the partogram gives an improved tool to handling a delivery if there is a halt in labor progress. Among the women who was included in the study and delivered operatively due to dysfunctional labor, over 80% had an increased level of lactate in amniotic fluid (>10.1mmol/l) when labor arrested. The duration of labor was also prolonged within the group of women with an elevated lactate level in AF.

Is there an unknown transport of lactate from the uterine tissue to the AF? Experimental studies with the purpose of finding an explanatory model for the transportation of lactate out of the myometrium and into the amniotic fluid have been performed (Akerud et.al 2009). Biopsies from uterine muscle, amniotic fluid samples, umbilical cord blood and biopsies from placenta of 60 women delivered by caesarean section were collected. The presence of lactate carrying protein was identified by immunohistochemical analysis. The proteins MCT1 and MCT4 were for the first time identified in human uterine tissue. MCT1 was found in all samples but MCT4 was found only in samples from the group of women that were diagnosed as having a dysfunctional labor. The MCT transport proteins bring lactate from uterine tissue to AF, and MCT4 is activated only in dysfunctional labor with a hypoxia of the tissue. Studies are underway to examine whether there are more systems for transport of lactate in myometrial tissue.

Recently a study was published where the association between a high concentration of lactate in amniotic fluid as a possible marker of uterine tissue hypoxia during delivery, pathologic cardiotocography trace (CTG), and adverse neonatal outcome at delivery was shown (Wiberg-Itzel et.al 2011). A sample of AF was collected just before delivery and the lactate concentration was analyzed blinded. An association between high lactate value in amniotic fluid just before delivery and adverse neonatal outcome at birth was confirmed. In the group with AF lactate concentrations greater than 10.1 mmol/L at the last sampling occasion before delivery, significantly more neonates had an adverse neonatal outcome at birth, resuscitation was performed more frequently, and a higher number of newborns were admitted to the neonatal intensive care unit. Two neonates with hypoxic–ischemic encephalopathy grade 2 were found, and both belonged to the group with a high concentration of lactate in amniotic fluid, whereas there were no newborns in the group with lower amniotic fluid lactate that developed hypoxic–ischemic encephalopathy.

In summary, it was found that the use of CTG together with an analysis of the lactate concentration in AF could be a promising and useful predictor of fetal outcome in labor. The method is easy, non-invasive, and safe for the mother and her unborn child. The findings have important clinical implications in view of the fact that children are still born with an unexpected adverse neonatal outcome, even with what is considered to be careful fetal surveillance

7.1 Ongoing study

Currently, a large collaborative prospective project between 10 European and one African clinic is running. In the "Dysfunctional labor study" data, saliva and amniotic fluid from 5000 primiparas and their deliveries is collected. This in a desire to gain more knowledge about the state called dystocia. The study is scheduled to continue until summer 2012.

8. Prelabor rupture of the membranes (PROM)

Prelabor rupture of membranes (PROM) is defined as `spontaneous leakage of AF prior to onset of labor´ with a gestational age of 37 weeks or more (WHO definition). Preterm PROM (PPROM) is ruptured membranes before 37 weeks of gestation. PROM is a relatively common event in obstetric practice, and the prevalence is reported to be 5-19% of all pregnancies (Hannah et al. 1996).

8.1 Clinical management of PROM

The management of PROM has been considered controversy since the 1950's. The modern era of this field began in 1966 with several reports that showed increased risk for both the mother and the fetus, when expectant management of PROM was undertaken. PROM without immediate onset of labor was considered to carry a high potential risk of incurring intrauterine infection (Shubeck et al. 1966; Webb 1967).

In the 1950's the perinatal mortality associated with PROM was estimated to range from 2.6% to 11%, and increased with the duration between PROM and delivery. The maternal mortality related to PROM, was reported to be 0.2‰. On the basis that PROM without immediate onset of labor was considered dangerous an aggressive approach to PROM was

advised in the 1970's and 1980's. Early induction and operative intervention were suggested, especially if labor had not started within 24 hours. One problem with this aggressive approach was failed inductions with concomitant increased frequency of caesarean sections.

Studies of women with PROM and unfavourable cervix status have been published (Kappy et al. 1979). A spontaneous onset of labor within 24 hours in 85% of the women with established PROM is presented. They also reported a reduced caesarean section rate with expectant management, and no evidence of increased neonatal infections.

In a large randomised trial of 5041 women with PROM they were randomly assigned to immediate induction of labor or expectant management (Hannah et al. 1996). The women were randomised to induction with oxytocin, vaginal PGE2-gel or expectant management up to four days after PROM. If labor had not started within four days, the women were induced with oxytocin or PGE$_2$ gel. The primary outcomes were neonatal infection and women's evaluation of their treatment. They found no significant differences between the study groups, and concluded that in both management groups a similar rate of neonatal infections (2-3%) and caesarean sections (10%) were found. Women evaluated early induction of labor more positively than expectant management.

A Swedish PROM study was conducted in the 1990's where 1385 women were included (Ladfors et al. 1996). The result showed a 13% prevalence of PROM after 34 weeks of gestation. They compared obstetric and neonatal outcome between two different expectant management groups, expectancy for 48 or 72 hours. The result showed a higher rate of spontaneous deliveries among nulliparas in the `late´ induction group compared with `early´ induction. The rate of instrumental delivery was lower in the `late´ induction group, but the rate of caesarean sections was similar. They concluded that expectant for 72 hours was to be recommended. Digital vaginal examination before onset of labor was not allowed in this trial. Low frequencies of maternal and fetal infections were found, and there were no differences between the groups.

False negative diagnosis with visual inspection at speculum examination was found to be 12%. No disadvantage, i.e. infections, was found for mother or child if the woman was sent home after a false negative speculum examination. They questioned the value of using biochemical tests in the management of women with suspected PROM. No comments were made on the assumed false positive diagnosis in women with suspect PROM. All women included in the trial had visible AF at examination, but 3.1% of them had intact membranes at delivery.

8.2 Historical review of PROM tests

In 1920's, it was found that vaginal pH turned from acid to neutral or alkaline when contaminated with amniotic fluid. In 1938 the nitrazine test was introduced, which measured pH in vaginal secrete within a narrower range. This method has been widely used all over the world.

The crystallisation pattern of AF was first described in 1950's. The crystallisation phenomenon, also called ferning or arborisation test is dependent on the relative concentration of electrolytes, proteins and hydrocarbonates in AF. The crystallisation test is nowadays still one of the most commonly used methods in clinical practice worldwide.

Fig. 4. Photo taken at microscopy (x 40) of AF from one woman included in the "lac-test" study.

Nile blue sulphate staining of the neutral lipid in cells from fetal sebaceous glands was described in 1960's. The cells turn orange as a consequence of the oxazone in Nile blue. The cells are single or grouped in clusters. Other cells, like vaginal squamous, and pus cells or erythrocytes stain blue. A limitation of this test is that these fat-containing cells are only present after 32 weeks of gestation.

In selecting a spectrum of tests to be used in doubtful instances of ruptured membranes, it was determined that a combination of these three tests described above would produce an accuracy of diagnosis approximating 93%.

8.3 Present tests of today

DAO test (DiAmine oxidase activity)

The DAO test was one of the first biochemical tests for PROM, and was developed during the 1970's. DAO is present in high concentrations in AF but is absent in normal vaginal secretions and urine. DAO is produced by placental decidual cells and increases during pregnancy. The method is reported to have a sensitivity of 84-100% and a specificity of 74-100%. The test was carried out with 10 ul of AF absorbed on a paper strip, and the test requires a scintillation counter. This method is not available today because of the toxic chemicals that are used in the analysis.

AFP test (Monoclonal antibody test kit)

AF also contains high concentrations of alpha feto protein (AFP) especially in preterm pregnancy. A monoclonal antibody assay method with high sensitivity and specificity was presented. However, they also reported that a false positive test may occur as AFP may cross weakened membranes in cases with chorioamnionitis or heavy blood contamination. This test is not used in clinical practice any more.

Fetal fibronectin (ROM-check)

Fibronectin is a large plasma glycoprotein. Three sub-types are available, of which one is feta derived. The concentration of fetal fibronectin in amniotic fluid is 5-10 times higher than in maternal plasma. In the 1990's many papers were published about fetal fibronectin and its usefulness to detect AF in women with suspect PROM. To use fetal fibronectin when detecting PROM is a sensitive test (97%) but a test with a very low specificity (27%). Additionally, in patients without rupture of the membranes, the interval between sampling and delivery was shown to be significantly shorter if fetal fibronectin was present. The conclusion was that the presence of fetal fibronectin in cervicovaginal secretions may be a good marker for impending labor rather than a good test for ruptured membranes. Today fetal Fibronectin is used in a combination with ultrasound, to detect the risk of premature delivery.

Insulin-like growth factor binding protein-1 (PROM-test™)

Insulin-like growth factor (IGF) is a peptide and is bound to a binding protein (IGFBP) in the blood circulation. IGFBP-1 is a placental protein and is present in much higher concentrations in AF as compared with serum, cervical mucous, urine or seminal plasma. A commercial kit, with monoclonal antibodies to IGFBP-1 attached to a small wand has been available since 1993 (actim PROM-test™). During the last decade, many papers have been published on the actim PROM-Test™. The sensitivity of the test is reported to be 71-100% and specificity 88-100%. It has been concluded that actim PROM-test™ is one of the most accurate diagnostic tests today in the diagnosis of suspected PROM. However, contamination of maternal blood or leakage of IGFBP-1 through stretched fetal membranes may cause false positive tests. A false negative result may occur if there is an inadequate sampling, intraamniotic infection, vaginal discharge, maternal blood loss, or prolonged time from rupture of membranes to application of the test. Gestatational age should not influence the test.

B-HCG in vaginal washing fluid

B-HCG is a glycoprotein produced exclusively by syncytiotrophoblasts in the placenta. Several studies have investigated β-HCG as a useful test for the diagnosis of PROM in the third trimester. These studies have shown a sensitivity of 68-100% and a specificity of 95-97%.

Amnisure®

In 1975, the placental alpha microglobulin–1 (PAMG-1) protein was isolated from AF. Antibodies were obtained against the protein and Amnisure® is an immunochemical method, used to measure the content of PAMG-1 protein in vaginal fluid, in cases with suspect PROM. Amnisure® has been available on the market since 2005. In a study which included 203 women with suspected PROM, a sensitivity of 98.8% and a specificity of 100% were found.

9. Lactate in AF, a new diagnostic tool when handling a suspect PROM

Lac-test, a good, reliable and useful clinical test for PROM with both a high sensitivity and a high specificity has been presented in several publications. The test is easy to use in the clinical situation with an answer immediately available at the bedside. A vaginal fluid lactate concentration of >4.5 mmol/l in women having a history of suspect PROM is shown

to be the best cut-off value to discriminate between visible/non visible AF at speculum examination.

300 Women attending the delivery ward in South General Hospital, Stockholm, with a suspected PROM were included in this prospective study (Wiberg-Itzel E et.al 2005). All women had a singleton pregnancy, a suspected history of PROM (scanty leakage of fluid from the vagina) after 34 weeks gestation and without uterine contractions. Cases with suspected PROM but with obvious pouring water were excluded. A speculum examination was performed, and the clinical management was based on whether AF was visible or not at examination. If AF was observed, induction of labor was planned after two days if labor had not started spontaneously. If AF was not seen and the pregnancy was otherwise uneventful, the woman was sent home with no further follow-up planned. Visible AF at speculum examination was regarded as `true´ ruptured membranes. The lactate concentration in vaginal secretions was analysed and registered by an independent nurse, and the value was concealed from the clinician in charge of the delivery ward.

In most cases, the diagnosis of PROM is obvious. The woman describes having experienced a history of limited water-like secretions from the vagina, and water is seen streaming down the legs or in pads. However, there still remain cases in which the history is strongly suggestive of ruptured membranes but at physical examination no AF can be seen. In these situations a speculum examination is recommended to confirm or exclude ruptured membranes. Studies have shown a false negative diagnosis with visual inspection of speculum examination to be 12% (Ladfors et al 1996). No increased morbidity (i.e. infection) is found in this group. In presented studies where only speculum examination was used, no comments were made on the assumed false positive group i.e. those where AF was thought to be seen but the membranes were obviously not broken. However, 3.1% of the women were reported to have signs of intact membranes at induction of labor, and could represent cases with false positive diagnosis as inspection was used.

When a speculum examination is performed, experience suggests that all ´water seen´ is not always ruptured membranes. Consequently, no visible AF can be a false negative observation, and visible AF can be a false positive one. If the woman has not started labor spontaneously within 48 hours after a diagnosed PROM, she will normally be exposed to induction of labor. 44% intervention rate (instrumental or emergency caesarean delivery) was shown in the induction group in this study. A particularly high frequency of intervention occurred in the group of women with visible AF but low lactate concentration ($<=4.5$mmol/l). This is an important finding, as reliable diagnosis might prevent unnecessary intervention, the `Lac-test´ is shown to be such a reliable test, which also is simple and handy in the clinical management.

To summarise the `Lac-test´ was found to be a reliable test with both a high sensitivity and a high specificity. Its ease of application makes it attractive in clinical practice.

9.1 Prediction of onset of labor

At term pregnancy PROM is often a part of normal parturition and most of the women with PROM will have a spontaneous onset of labor within a limited period of time. PROM occurs in 5-19% of all patients at term and is followed by spontaneous onset of labor in 60% within

24 hours and in 95% within 72 hours. However, it is crucial to diagnose ruptured membranes. 10% of pregnant women at term attend hospitals with suspected PROM, and to have the possibility to predict those who will start labor spontaneously would clearly simplify management (Wiberg-Itzel et al. 2006). A good prediction is also appreciated by the parturient.

The time to onset of labor was in this work essentially similar among women with lactate concentration of >4.5mmol/l in vaginal fluid. In contrast, women with lactate concentrations <4.5 mmol/l appeared to have longer time to spontaneous onset of labor (median time 54 hours) from the time of examination. These findings lend support to the view that it is the rupture of the membranes (ROM) which is crucial to diagnose, when estimating the probability of spontaneous onset of labor within one or two days.

In clinical practice there is a lack of any adequate predictor to identify women with spontaneous onset of labor within a certain time limit. Transvaginal ultrasonographic measurement of cervical length is one method which is used in clinical practice. However, this method is mainly used in cases with a risk of pre-term labor. No clear, rational and evaluated strategy for daily practical use has emerged.

In this study 54 % of all the women included were in labor within 24 hours. Among those with a lactate concentration > 4.5 mmol/l, 88% had spontaneous onset of labor < 24 hours, compared with 21%among those with lower lactate value. However, in the group where amniotic fluid was not visible and the lactate level was low (<4.5 mmol/l), only 15% had started labor within 24 hours. By using lactate concentration > 4.5 mmol/l as cut-off, a total number of 83%would be correctly classified as to whether they were going to be in labor within 24 hours or not.

Summarising suggests that cases with suspected PROM (not water streaming down the woman's legs) should primarily be correctly diagnosed with the `Lac-test´, to avoid false positive tests at inspection and unnecessary intervention, and to obtain a good prediction of onset of labor.

9.2 PPROM

Preterm prelabor rupture of membrane (PPROM) is defined as 'rupture of the fetal membranes prior to onset of labor in a patient who has a gestational age of less than 37 weeks'. PPROM occurs in approximately 3–5% of all pregnancies and accounts for one-third of all preterm births. PPROM is associated with risks of preterm delivery and with substantially increased risks of perinatal morbidity and mortality.

An accurate diagnosis of PPROM is critical to both long- and short-term health and survival for the baby. The absence of a 'gold standard' for the diagnosis of PPROM has stimulated us to search for a clinically applicable marker of PPROM and a marker to predict onset of preterm labor (Wiberg-Itzel et.al 2009).

We have previously shown that a positive 'LAC test', that is a lactate concentration >4.5 mmol/l in vaginal fluid, is a reliable test for rupture of the membranes in pregnancies of 34 weeks of gestation or more. We have also found a significant association between a positive

LAC test and spontaneous onset of labor within 48 hours in late gestations, that is >34 weeks.

Of the 81 women included in this study, 45 had a gestational age less than 34 weeks at the time of examination. Among these, 11 women (24%) had a lactate concentration of >4.5 mmol/l (positive LAC test), of whom 9 (82%) were in active labor within 48 hours. 'False negatives' (negative LAC test but delivered <48 hours) occurred in 0 of 34 women in this subgroup.

A prediction of spontaneous onset of labor is even more valuable in preterm pregnancies, when antenatal steroids may be administered, and women may be referred to tertiary level of medical care. The publication showed that lactate determination in vaginal fluid seems promising as a tool to predict onset of labor within 48 hours even in women with suspected PPROM. A positive LAC test (>4.5 mmol/l) was more strongly associated with spontaneous onset of labor than visible AF.

10. Conclusion

Failure of progress in labor contributes to the increased frequency of caesarean section worldwide. If we are attempt to address this problem it is necessary to understand the reasons why this occurs, identify the women most likely to develop dystocia in labor and apply timely and appropriate interventions to correct inefficient uterine action when possible, thereby improving outcome for mothers and their babies.

To be able to get a correct diagnose in cases with suspect PROM, to avoid false positive tests, unnecessary intervention and to obtain a good prediction of onset of labor, in term as well as in preterm deliveries, is very appealing.

Our hope is that lactate value in AF will be a new and very useful diagnostic tool in obstetrical care.

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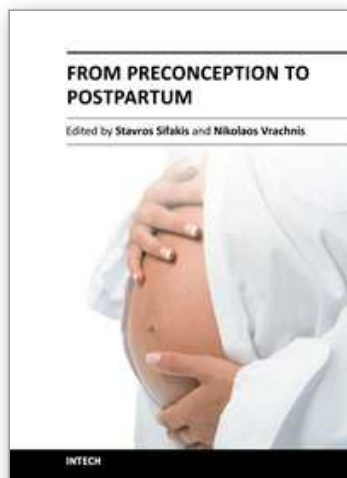
From Preconception to Postpartum

Edited by Dr. Stavros Sifakis

Obstetrics is evolving rapidly and finds itself today at the forefront of numerous developments. Providing selected updates on contemporary issues of basic research and clinical practice, as well as dealing with preconception, pregnancy, labor and postpartum, the present book guides the reader through the tough and complex decisions in the clinical management. Furthermore, it deepens the scientific understanding in the pathogenetic mechanisms implicated in pregnancy and motivates further research by providing evidence of the current knowledge and future perspectives in this field. Written by an international panel of distinguished authors who have produced stimulating articles, the multidisciplinary readers will find this book a valuable tool in the understanding of the maternal, placental and fetal interactions which are crucial for a successful pregnancy outcome.

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