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Post-term pregnancy

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OVERTIDIG SVANGERSKAP

Overtidig svangerskap er å betrakte som et risikosvangerskap. Studier har vist at det ved overtid er økt risiko for død i mors mage og i nyfødtperioden. I mange land settes derfor fødselen i gang en uke etter at terminen er passert, men i Skandinavia er det tradisjon for å la svangerskapet fortsette 2-3 uker etter at terminen er passert. Studier har vist at det å sette fødselen i gang også er forbundet med komplikasjoner for mor og barn. Behandlingen av det ellers ukompliserte overtidige svangerskap er kontroversiell.

Avhandlingen består av 4 delstudier.
I den første studien undersøkte vi hvordan det gikk med mor og barn i forhold til hvilken svangerskapsuke fødselen skjedde. Vi undersøkte også om det var forskjellige resultater for mor og barn om fødselen startet av seg selv eller ble igangsatt. Alle kvinner som fødte etter 37. svangerskapsuke ved St.Olavs Hospital i perioden 1990-2001 ble inkludert. Resultatene viste at komplikasjoner hos mor varierte med svangerskapslengden, og var lavest en uke før termin og høyest når svangerskapet var overtidig. Komplikasjoner for barnet varierte med svangerskapslengde bare hvis fødselen startet av seg selv. Igangsetting av fødsel var en risiko for komplikasjoner uavhengig av svangerskapslengde.

Den andre studien sammenlignet sykelighet hos barna og komplikasjoner hos mor hvis fødselen ble satt i gang en uke over termin eller svangerskapet ble kontrollert hver 3. dag til hun var nesten 3 uker over terminen. Kvinnene trakk lodd om hvilken gruppe de skulle komme i, og til sammen deltok 508 kvinner. Sykeligheten hos barna var den samme i begge grupper. Det var flere raske fødsler i gruppen som fikk fødselen igangsatt, men det var det ingen forskjell på forekomsten av komplikasjoner mellom gruppene. Keisersnittfrekvensen var lav.

Kvinnene som deltok i den andre studien ble intervjuet om sitt syn på overtidig svangerskap når de ble inkludert. Dette ble gjentatt 6-8 måneder etter fødselen, og de ble da også spurt om hvilke erfaringer de hadde gjort seg og hvordan de ønsket å bli fulgt opp i et evt. fremtidig overtidig svangerskap. En uke over termin svarte 74% at de ønsket å få fødselen igangsatt. De fleste (84%) som fikk fødselen igangsatt rapporterte at dette var en positiv opplevelse, og 74% ønsket å bli igangsatt hvis de skulle bli overtidige i et fremtidig svangerskap. Bare 38% av de som kom i ventegruppen ønsket å vente. I gruppen som ble igangsatt var det flere raske fødsler, og kvinnene anga at riene var mer intense og hyppige i denne gruppen sammenlignet med ventegruppen.

I den siste studien så vi på data fra Medisinsk Fødselsregister for alle fødsler etter 41 uker i Norge i perioden 1999-2005. Vi ønsket å studere forekomsten av fosterdød i mors mage og død i tidlig nyfødtperiode og regne ut hvor mange fødsler man måtte sette i gang for eventuelt å unngå 1 dødsfall. Forekomsten av dødsfall var lav, men økte med svangerskapslengden. Ved uke 41 må man sette i gang > 500 fødsler for å unngå 1 dødsfall, ved uke 43 < 200. Hvis vi i Norge skal sette alle fødsler i gang ved 41 uker, vil dette medføre > 14.000 igangsettinger i året.

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1 Acknowledgements

2   List of papers

This thesis is based on the following papers:

I   Study 1:

        Outcomes of pregnancy beyond 37 weeks of gestation.

        Runa Heimstad, Pål R. Romundstad, Sturla H. Eik-Nes, Kjell Å. Salvesen.

        Obstet Gynecol. 2006 Sep;108(3 Pt 1):500-8.

II   Study 2:

        Induction of labour or serial antenatal fetal monitoring in postterm pregnancy: A
        randomized controlled trial

        Runa Heimstad, Eirik Skogvoll, Lars-Åke Mattsson, Ole Jakob Johansen, Sturla H.
        Eik-Nes, Kjell Å. Salvesen.

        Obstet Gynecol 2007;109(3):609-17.

III   Study 3:

        Women's experiences and attitudes towards expectant management and induction of

        labour for post-term pregnancy.

        Runa Heimstad, Pål R. Romundstad, Jon Hyett, Lars-Åke Mattsson, Kjell Å. Salvesen.
        Acta Obstet Gynecol Scand 2007,1-7, iFirst Article

IV   Study 4:

        Induction of labour for post-term pregnancy and risk estimates for intrauterine- and

        perinatal death.

        Runa Heimstad, Pål R. Romundstad, Kjell Å. Salvesen.

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3 Abbreviations

AFI	Amniotic fluid index
AGA	Appropriate for gestational age
BMI	Body Mass Index
BPD	Biparietal Diameter
CI	Confidence Interval
CMPP	Canadian Multicenter Post-term pregnancy
CRL	Crown rump length
CTG	Cardiotocography
DHEA-S	Dehydroepiandrostendion-sulphate
EDD	Estimated Date of Delivery
FHR	Fetal heart rate
FL	Femur length
IUFD	Intrauterine fetal death
IVF	In vitro fertilization
LMP	Last Menstrual Period
MMP	Matrix metalloproteinase
NICU	Neonatal Intensive Care Unit
NNT	Number needed to treat
OR	Odds Ratio
PGE	Prostaglandin E
PGF	Prostaglandin F
RCT	Randomised controlled trial
RR	Relative Risk
SD	Standard Deviation
SGA	Small for Gestational Age
WHO	World Health Organization

4   Introduction

The most famous post-term delivery in the past was the delivery of Princess Charlotte Augusta of Wales in 1817. She was the only eligible heir to the British throne, and when her pregnancy was announced, the entire nation was closely following the most important event of that time.

At approximately 43 weeks her water broke and labour soon began spontaneously. Contractions were weak and the first stage of labour lasted more than 50 hours. Gradually, the fluid became meconium stained. After 24 hours in the second stage of labour and after five hours of active pushing, she spontaneously delivered a stillborn boy. The baby appeared to have been dead for several hours. During the third stage, placenta was retained, and she had a post-partum haemorrhage from uterine atony. Princess Charlotte died approximately six hours after delivery.

Three months later her obstetrician, Dr. Croft, committed suicide, unable to bear the burden of the responsibility for the death of the British heir to the throne. [1]

As this event resulted in the death of an infant, the mother and her physician, it has historically been referred to as the *"The Triple Obstetric Tragedy."*

Princess Charlotte Augusta of Wales

4.1 Definition

Post-term pregnancy is defined by WHO and FIGO as a pregnancy with a gestational length of 294 days or more (i.e. 42 completed weeks or more).[2, 3] In a survey to all birth units in Norway in 2003, only 6 of 43 units defined post-term pregnancy according to WHO, and the majority of units (37/43) defined post-term pregnancy as 296 days or more.[4] In some international studies, however, post-term is used for women at a gestational age of 41 weeks.[5-7]

Postmaturity (or postmaturity syndrome) is a clinical condition describing an infant born post-term with a poorly functioning placenta. The infant usually appears long and thin, with dry scaly skin and long finger nails, and in some cases there are meconium staining of the skin and membranes. It has been suggested that postmaturity syndrome is really just fetal growth restriction in post-term fetuses.[6]

4.2 Gestational length

4.2.1 Estimation of day of delivery

Hermann Boerhaave (1668-1738) was Professor of Botany and Medicine at the University of Leyden. He was the first to set down the calculation from which Naegele's rule evolved. In the Academic lectures of Hermann Boerhaave "On conception" (published in 1744), the relevant passage translates as follows: "Women for the most part are impregnated after the end of their period: Numerous experiments undertaken in France confirm this: for of one hundred births altogether, ninety-nine came about in the ninth month after the last menstruation by counting one week after the last period and by reckoning the nine months of gestation from that time."[8]

Franz Carl Naegele (1778-1851), Professor of Obstetrics at the University of Heidelberg, quoted this statement in his text from 1812 and also made his own observations on the ability and timing of conception in women. Naegele's rule assumes a 28-day-cycle with ovulation on day fourteen. By adding seven to the first day of the last menstrual period and counting back three months the expected date of confinement is reached. This is the method by which Naegele's rule has been calculated during this century. It is possible that Boerhaave and Naegele have been misinterpreted, and that their original rule may have been

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to add seven days to the end rather than the beginning of the last menstrual period. This would achieve the same result as ultrasound with respect to induction of labour for post-term pregnancy.[8]

However, only 10-40% of women can recall the exact date of the first day of their last menstrual period (LMP), and the LMP estimated date of delivery (EDD) might be biased of amenorrhea, irregular menstrual cycles or use of oral contraceptives.[9, 10] Due to the unreliability of this method, new technology and methods have been introduced to estimate date of delivery during the last decades. Ultrasound estimation of gestational age is based on the assumption that early fetal growth is uniform in all fetuses. Blaas et al. showed that first trimester embryos have parallel growth irrespective of their menstrual age, implying that embryos of the same size have approximately the same age.[11] The first reliable method of predicting gestational age based on ultrasonic measurement of the biparietal diameter (BPD) was described in 1969 by Campbell.[12] Several studies have indicated that ultrasonic measurements of BPD, crown-rump length (CRL) or femur length (FL) are better than the LMP to predict the day of delivery.[13-16] There are several formulas and methods of estimating the date of delivery by ultrasound, and the best method is still a matter of discussion.[17-19] Ultrasound is also found to be a reliable method in pregnancies conceived with assisted reproductive techniques, and assessment of gestational age from the time of IVF, CRL and BPD showed equally high agreement between the three methods.[20] Today ultrasound is the method of choice for dating pregnancy, and the technology is available in most countries worldwide.[21] In Norway this is an offer provided by the health care system and 97% of pregnant women attend the routine ultrasound screening around 18 weeks.[10]

Several studies have demonstrated that LMP dates systematically overestimate gestational age compared with scan dates, suggesting that most pregnancies considered to be post-term according to LMP are in fact misdated.[10, 22, 23] The most prominent difference in the distributions of births is the absence of the tail of post-term births for ultrasound dated pregnancies.[10] In a study by Blondel et al., the proportion of births ≥42 weeks was 6.4% when the LMP method was used, but only 1.9% when ultrasound was used.[24] Similar results were found in a Norwegian study by Tunon et al. (10% versus 4%, p<0.001).[10] Routine ultrasound examination in early pregnancy results in reduced incidence of induction of labour for apparent post-term pregnancy.[25, 26] In a study by Eik-Nes et al. there was a 70% reduction in the incidence of induced labour for apparent post-term pregnancies for women who were routinely screened with ultrasound compared to women who did not receive ultrasound routinely.[27]

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In addition to LMP and ultrasound, gestational age can be determined by physical examination of the uterus, when the pregnancy test was first positive or a combination of several different methods. Some studies on post-term pregnancy have used several methods to estimate gestational age, which makes it difficult to interpret the results.[28, 29] In the Canadian Multicenter Post-term pregnancy trial (CMPP) the following methods to determine gestational age was used: according to LMP if the woman had had regular cycles without use of oral contraceptives or the known date of conception, confirmed by a pregnancy test at < 6 weeks, a physical examination at ≤ 20 weeks or ultrasound at ≤ 26 weeks; by ultrasound at ≤ 26 weeks if LMP was uncertain; or by ultrasound on two occasions at ≤ 26 weeks that resulted in consistent estimates of gestational age, if LMP was unknown.[30]

4.2.2 Duration of pregnancy

For many centuries it has been accepted that the normal gestational period for humans is nine calendar months. The more exact duration of a pregnancy has been topic for research and discussion for years.[8, 15, 31] WHO has defined the length of pregnancy to be 280 days, which is a slight modification of Naegele's rule.[2] However, several studies suggest that duration of pregnancy should be 281-283 days.[10, 31] Deliveries are not normally distributed. Thus, mean values of duration of pregnancies must be inaccurate. The median value implies that 50% deliver before and 50% after that day, whereas the mode value represents the day most women deliver. In the study with data from the Swedish Birth Registry from 1976-1980, the mean duration of pregnancy was 281 days, mode 282 days and median 282. In a Danish study the median gestational age at delivery, estimated by ultrasound in the first and second trimesters and by corrected LMP according to cycle length, were 282, 280 and 283 days respectively.[32] When dating methods are compared, elective deliveries may influence mean, mode and median values of pregnancy length. To avoid this problem some studies only include deliveries with spontaneous onset of labour. A "time to event" analysis with censoring elective deliveries at the time they occur can also be used. In a study by Smith, the median time to delivery from the Kaplan-Meier product estimate was 283 days.[33] A new computer-based estimation of "time to delivery" and estimation of date of delivery has been developed by Eik-Nes et al. (article in press, Ultrasound Obstet Gynecol).

Duration of pregnancy varies in different populations. One theory is that cervical ripening occurs in a timely, species specific manner in which programmed cell death

(apoptosis) may play a role. Apoptosis may be a genetically timed event and could explain the variation of pregnancy length, including the variation between different ethnic groups.[34]

Likewise, duration of pregnancy may vary with the gender of the fetus, although results from different studies are inconsistent. Some have found no difference, whilst others have found that boys tend to be born earlier.[31, 33] In comparison with dating by last menstrual period, the EDD in male-gender pregnancies has been found to be adjusted by ultrasound fetometry to be earlier, and in female-gender pregnancies to be later, with a mean difference of 1.50 days.[35]

In a survey to all birth departments in Norway in 2003, all departments defined 282 days as duration of pregnancy.[4] In daily clinical practice "Snurra" has been widely used for estimating gestational age in Norway. "Snurra" is a practical facility prepared by Eik-Nes and Grøttum and is based on duration of pregnancy of 282 days.

4.2.3 Discrepancy between LMP and EDD by scan

The EDD estimated by ultrasound is usually later than the LMP date. Some studies report that fetuses who are smaller than expected at a second trimester ultrasound examination have a higher risk for bad outcome, but this is disputed by others.[36-38] Tunon et al. compared groups where the EDD by scan differed more than 14 days or less than 7 days from the LMP estimate.[37] They reported no statistically significant differences of perinatal morbidity and mortality. However, they did report a RR of perinatal death of 2.07 with a CI 0.93-4.61, and suggested further studies, as an extensive discrepancy in gestational age could be a marker for fetuses that might benefit from closer monitoring. Nakling and Backe found that a discrepancy between LMP and EDD by scan of more than 14 days was a risk factor for preterm delivery, birth-weight < 2500 g, SGA and perinatal death.[38] It has been claimed that a large discrepancy between LMP and EDD by scan may indicate early disturbances in fetal/placental development and growth restriction. The risk in one study increased significantly with pregnancy length, and at least a part of the increased risk for poor pregnancy outcome in adjusted pregnancies was due to not recognizing true post-term pregnancies.[39]

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4.3 Etiology

The etiology of post-term pregnancy is not known. Since we do not know the mechanisms for initiating spontaneous labour, the reasons for post-term pregnancy will probably remain unsolved for years to come. Multi-factorial causes have been postulated since explanatory models are unproven.

4.3.1 Risk factors for post-term pregnancy

The duration of pregnancy tends to be shorter if the fetus is a boy,[31] but a pregnancy with a male fetus is also a risk factor for post-term pregnancy.[40] The uncorrected OR for having a male baby at ≥ 42 weeks was 1.41 (95% CI 1.33–1.49) in one study.[41] After adjusting gestational age by ±0.75 days, the OR was reduced to 0.90 (95% CI 0.84-0.95).[35] The risk for labour induction was increased in male-fetus pregnancies delivered after 41 weeks when gestational age was corrected for fetal gender.[41]

In a Swedish study, the risk of post-term pregnancy also increased if the woman was primiparous.[42] It seems that maternal age is a risk factor. The incidence of deliveries beyond 41 weeks is reported to increase as maternal age increase, but also among teenagers.[42, 43] For multiparous women there is a tendency to deliver post-term more often after a long interpregnancy interval.[44] However, the risk of recurrence of post-term delivery can be reduced when the first and second child have different fathers.[45]

Only a few studies address specific environmental, occupational or life-style exposures and post-term pregnancy. Occupational exposure to ethylene oxide has been reported to increase the risk of both preterm and post-term birth, and after the Chernobyl accident an increase in post-term births was reported in Ukraine and Belarus.[46] Several studies have demonstrated a relation between fish intake and duration of pregnancy, and a Danish study reported that a fish free diet was associated with a reduced risk of post-term delivery.[47] Also smoking has been found to reduce the risk of post-term delivery, and this was most pronounced if gestational age was based on ultrasound.[48] Post-term pregnancy has also been found to be associated with obesity (BMI > 30).[49]

4.3.2 Genetics

Duration of pregnancy varies with ethnicity. The average length of pregnancy is found to be about 5 days shorter in black populations than in white populations.[50] This implicates that the post-term complications and postmaturity syndrome may occur at a shorter gestational age in black populations.

The recurrence risk of post-term delivery can be reduced when the first and second child have different fathers.[45] This suggests that paternal genes may play a role for the gestational length. However, changing a partner is also likely to include changes in environmental factors and a longer interpregnancy interval, and this could be the explanation rather than the paternal genes. In a large Danish study the duration of the first pregnancy of both female and male twins were studied. The results suggested that 23-30% of post-term pregnancies were due to genetic factors, and that only maternal genes influenced pregnancy length.[51]

Studies across generations are difficult because the methods of estimating EDD have changed over time, and the prevalence of post-term pregnancies may vary over generations due to environmental factors. Study results are somewhat conflicting. One study found that if a mother delivered post-term, the relative risk (RR) was moderately increased for her daughter to deliver post-term (RR 1.3, CI 1.0-1.7).[52] Other studies concluded that variability in gestational age could not be determined by genetic factors.[53] In a recent Norwegian study, both paternal and maternal gestational age at birth were found to be related to gestational age of their offspring. However, the association in gestational age was much stronger between mother and child than between father and child.[54] Individual risk factors seem to be more important, as a previous post-term pregnancy increase the risk of a subsequent post-term pregnancy 2-3 times.[52]

4.3.3 Hormones

Some congenital anomalies (anencephaly, trisomies 16 and 18) are associated with post-term delivery. This also applies to conditions that alter the fetal adrenal-pituitary axis (absence of the fetal pituitary or fetal adrenal hypoplasia).[46] The explanation may be that these conditions lack the high concentrations of estrogen seen in normal pregnancies. Some studies have found that maternal levels of estradiol and estriol increase at the time of delivery,[55] whereas others

found no difference.[56] Some have proposed that the estrogen/progesterone-ratio is important for the start of labour, and that the changes in steroid hormone concentrations may occur locally within intrauterine tissues, since both fetal membranes and decidua can syntesize and metabolize estrogen and progesterone.[55]

Progesterone is important for the maintenance of pregnancy, and in many species a progesterone withdrawal will cause delivery.[57] However, there is no decline in plasma progesterone levels in humans at the time of parturition, and progesterone levels continue to increase in pregnant women up to the time of delivery. Nevertheless, a withdrawal of functioning progesterone may be linked to the initiation of the parturition even in humans. Human amnion and chorion have the capacity to convert progesterone to the inactive 20α-dihydroprogesterone.[58] The metabolic inactivation of progesterone by fetal membranes increases with advancing pregnancy and the onset of parturition.[57] This supports the hypothesis that progesterone withdrawal could be mediated by target tissue inactivation. Progesterone withdrawal could also occur through the action of endogenous anti-progesterone. Some studies have demonstrated that anti-progesterone (mifepristone - RU486) can be used to induce labour and ripen the cervix.[59] This is questioned by others.[60] Thus, the role of progesterone in the endocrine regulation of human parturition is still unclear.

It has been proposed that estrogen formed from fetal adrenal androgen is central in the initiation of parturition.[61] When androstenedion infusion was given to pregnant monkeys, an increased level of estradiol and oxytocin were observed, and delivery occurred earlier compared with a control group.[61] A study of the hormonal status in a group of women that underwent induction of labour found a higher level of DHEA-S in the group with favourable cervix than in the group with unfavourable cervix, while the level of estradiol, estriol, cortisol and progesterone were the same.[56] A correlation between DHEA-S and cervical ripeness has later been demonstrated in other studies, and low levels of DHEA-S have been found to predict a need for oxytocin augmentation during labour and unsuccessful labour induction.[62, 63]

As far as we know, there are no studies on hormonal levels in post-term pregnancies. Post-term women may have different hormone status compared with women who deliver at term or preterm. Unpublished data from the Norwegian SGA-study, suggests that women with high levels of androgens during pregnancy tend to deliver earlier than women with low androgen levels, and in particular if the fetus is growth restricted (Carlsen-personal communication).

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4.3.4 Start of labour

A fundamental question in human physiology is still unclear: How is the timing of parturition regulated, and what triggers the cascade of events leading to delivery?

In addition to hormones, there are numerous physiological, biochemical and biomechanical factors involved in parturition. The process probably involves the mother, fetus, placenta, membranes, cervix and myometrium.

The association between a father's gestational age at birth and his offspring's gestational age at birth suggests that paternal genes are involved.[54] This supports a hypothesis that the fetus is involved in the onset of labour.

The process of cervical ripening is complex, and only fragments of the process will be discussed here. Anatomical and morphological changes are considerable, and a predominate change in cervical ripening is the rearrangement of collagen.[34] Connective tissue containing collagen and elastin has a characteristic property to reorganize its structure in response to a mechanical stretch or force. During the first stage of labour, mechanical stretching of the cervix occurs with the force of uterine contractions. The mechanical manipulation causes increased levels of prostaglandin $F_{2\alpha}$ which in turn will increase uterine contractions – a physiological response called the Ferguson's reflex.[34] The mechanical pressure exerted on the cervix of the presenting part of the fetus, cause both realignment of the collagen and stretching of the elastic fibres.[34] Collagenases and other matrix metalloproteinases contribute to the reorganization of collagen and cervical ripening. It has been proposed that DHEA-S causes collagenase activation and thereby remodelling of uterine connective tissue.[62] The changes in the extracellular matrix, including a 30 % reduction of the collagen concentration, a 50% decrease in the small proteoglycan decorin and a 15% increase in the large proteoglycan versican contribute to the softening of the cervical tissue.[64] Versican has the capacity to attract water and bind hyaluronan, resulting in disintegration of the collagen bundles and a change in the physical properties. This will produce a soft and elastic tissue and facilitate dilation of the cervix. Decorin, the major proteoglycan in the human cervix, influences collagen fibrillation and rearrangement, and thus, the stiffness of the cervix.[65] Several studies have demonstrated the involvement of different types of matrix metalloproteinases in the cervical ripening process. MMP–1, MMP-3 and MMP-8 were found to be involved in one study,[64] and MMP-2 and MMP-9 in another study.[66]

It has also been proposed that cervical ripening can be regarded as an inflammatory reaction. The levels of mRNA encoding IL-6, IL-8 and granulocyte colony-stimulation factor

are increased 100-fold during cervical ripening, and prostaglandin degradation occurs.[65] Prostaglandins are involved in the onset of human parturition, and in particular the E and F series have well-established roles in labour. PGE2 is a potent uterotonic agent produced within the amniotic cavity in increased amounts before and during labour and it plays a central role in the cervical ripening process. This will be discussed later in the section about induction of labour. A newly published study suggests that also D-synthase might play important physiological roles in the placenta and potentially having a regulatory role in the processes of parturition.[67] There are, however, several unknown factors, and the knowledge of the complicated physiological process of parturition is still limited.

4.4 Prevalence of post-term pregnancies

The reported prevalence of post-term pregnancies vary between 5.5% and 9.5% in different studies, countries and time periods.[68, 69] In Scandinavia, the prevalence has been stable around 7-8% during the last years.[27, 28]

Some studies report decreasing prevalence rates, possibly due to more reliable dating methods or a change in obstetric management towards a more aggressive induction policy. In Spain the prevalence decreased from 8.1% in 1980 to 5% in 1992.[70] The same trend was seen in Australia, where prevalence of deliveries at or beyond 42 weeks was 4.6% in 1990, and 2.8% in 1996.[71] In an Australian study a general shift towards births at earlier gestational ages was reported.[71] This contrasts the situation in Norway, where the proportions of deliveries at different gestational ages have been relatively stable over the last decades. However, the proportion of deliveries beyond 42 weeks has decreased even in Norway, especially after 1992. (Table 1)

Table 1. Proportions of deliveries (%) beyond term in Norway 1968-2002 according to statistics from the Medical Birth Registry of Norway.

	1968	1972	1976	1980	1984	1988	1992	1996	2000	2002
40	27,2	26,9	27,3	27,3	26,9	26,3	25,6	26,3	24	23
41	20	20,8	21,3	21,4	21	20,3	20,1	20,7	18	18
42	9,2	10,4	10,6	10,4	10	9,5	9,6	10,1	9	8,7
+43	5,1	5,9	5,2	4,4	4,6	4,6	4,9	2,7	2,8	2,7

4.5 Complications of post-term pregnancy

The incidence and severity of complications vary from study to study, usually reported as the number of complications per 1000 deliveries.[28, 29, 72] However, as pointed out by Yudkin et al., fetuses at risk of stillbirth at a specific gestational age must include all live fetuses at risk at that particular gestational age.[73] He argues that the number of stillbirths per ongoing pregnancies is the appropriate risk estimate to be used. Thus, stillbirths and early neonatal deaths should be reported separately and appropriate denominators must be used.[74] The most frequently cited study on post-term pregnancy and stillbirth risk is a study by Hilder et al.[75] The stillbirth rate per 1000 ongoing pregnancies was found to increase from 0.35 at gestational week 37 to 2.12 at week 43, whereas the stillbirth rate per 1000 births decreased from 6.2 to 1.5 from gestational week 37 -43.[75]

Several studies using modifications of Yudkin's model have been performed.[76-79] An example of how Yudkin's model can alter conclusions within a dataset was seen in a Swedish study. The authors reported an increased risk of stillbirths in post-term pregnancies for primiparous, but not for multiparous women when the denominator was per 1000 deliveries.[28] By using the model of Yudkin on the same dataset (per ongoing pregnancies), increased risks were found in both groups.[80, 81]

Yudkin's model is useful to assess the short term risk of stillbirth.[82] The short term risk of stillbirth is interesting for obstetricians in their daily clinical risk assessment and counselling of post-term women. The original Yudkin model risk estimated a two-week period and a revised model used a one-week period. A more useful clinical approach would be to give risk estimates for a few days only. The information a pregnant woman would like to know is the risk for stillbirth at her particular gestational age and the increased risk if the pregnancy is allowed to continue for a few more days.

4.5.1 Perinatal and neonatal mortality

Stillbirth and neonatal death are of course worst case scenarios, and post-term pregnancy increases the risk of both events.[22, 28, 75, 83] Several studies have reported increased stillbirth rate from 41 weeks gestation,[42, 75, 84] and some have reported increased risk from 40 weeks gestation.[77] In a study from the National Swedish Medical Birth Registry, the odds ratio for fetal death was 1.5, 1.8 and 2.9 at 41, 42 an 43 weeks respectively compared to 40 weeks.[42]

Some studies report a summarized risk of stillbirth and neonatal death, which was slightly increased in post-term pregnancies compared to term pregnancies (OR 1.36; 95% CI 1.08-1.72).[85] Other studies have divergent conclusions, and some found that neonatal mortality was independent of gestational age.[29, 42]

It has been suggested that the increased mortality rate in post-term pregnancies is due to fetal growth restriction. One study found that fetal growth restriction was associated with significantly higher odds ratios for both fetal and neonatal mortality rates for every gestational age between 40 and 43 weeks, with odds ratios ranging from 7.1 to 10.0 for fetal death and 3.4 to 9.4 for neonatal death.[42] In a large Swedish study of more than 500.000 deliveries, the increased risk of stillbirth in post-term pregnancies was found to be associated with an increased rate of small for gestational age infants (SGA)(OR 10.56; 95% CI 6.95-16.05).[72] When SGA-births with congenital malformations were excluded, the risk of infant death decreased considerably.[72] In this study there was no significant increase in stillbirths or infant deaths among appropriate for gestational age infants born post-term compared to those born at term. In a study of variables associated with perinatal mortality in post-term infants in a ten year cohort of Norwegian births, SGA births had a risk of perinatal death almost six times greater than non-SGA births (adjusted RR 5.68; 95% CI 4.37-7.38).[6] The second most influential risk factor was maternal age 35 years or older (adjusted RR 1.88; 95% CT 1.22-2.89). [6]

4.5.2 Neonatal morbidity

Since the risk of fetal and infant mortality is low, a possible association between morbidity and post-term pregnancy is more of concern in daily clinical work. A number of neonatal complications have been associated with post-term pregnancy, e.g. meconium aspiration, NICU admission, fetal distress and convulsions.

Several studies have reported an increased risk of meconium aspiration, which in turn is associated with neonatal morbidity.[72, 85-87] NICU admission rate is increased for post-term neonates.[29, 88] Fetal distress has also been associated with post-term pregnancy.[85, 89, 90] The diagnosis of fetal distress is usually based on low Apgar scores or fetal acidemia. The risk of low Apgar score at five minutes has been found to be increased in post-term compared to term deliveries in some,[72, 87, 91] but not all studies.[29] Umbilical artery pH <7.0 was associated with post-term pregnancy in one study,[92] while others were unable to confirm this.[29] In a study of

Caughey et al. the adjusted OR for pH < 7.0 was 1.65 at 41 weeks and 2.31 at 42 weeks when gestational week 39 was used as reference.[92] Further, they found that umbilical cord pH decreased with increasing gestational age. This is in accordance with the results in a study by Kitlinski et al.[92, 93] Kitlinski et al. proposed that gestational age adjusted cut-off levels of pH should be used to avoid a diagnosis of acidosis when umbilical artery pH are within the normal limits of a particular gestational age.

A study by Caughey et al. did not have sufficient power to demonstrate statistically significant differences when each complication was studied separately according to gestational age. However, the summarized complication risk increased from 40 weeks gestation.[92] Other complications found to be associated with post-term deliveries are convulsions, birth trauma (skull fracture, plexus brachialis injuries), intracranial haemorrhage, neonatal sepsis and respiratory distress syndrome.[85] Olesen et al. found increased OR for these complications in post-term births (1.22-1.90) compared with term births.[85]

Most neonatal morbidity measurement instruments are developed for preterm neonates. In most studies on post-term deliveries, neonatal morbidity was not properly defined. In general, the measurements used were expressions of morbidity, such as low Apgar score and NICU transfer. The largest reported randomised trial on post-term pregnancy is the Canadian Multicenter Post-term Pregnancy Trial (CMPP).[30] The trial used a novel neonatal morbidity index. The morbidity index was defined after the first 1500 infants had been born, and a consensus conference was held to define measures of neonatal morbidity. Outcome measures for neonatal morbidity used in a recent Cochrane review were: Birth asphyxia (as defined by trialists), admission to NICU, neonatal convulsions, neonatal encephalopathy, use of anticonvulsants, meconium aspiration syndrome, pneumonia, Apgar score less than seven at five minutes and neurodevelopment at childhood follow-up.

4.5.3 Long term outcome for children

There are very few studies on follow-up of children born post-term. In a study from Toronto, 184 normal term controls and 129 infants born beyond 294 days were followed for 1-2 years to examine the influence of prolonged pregnancy on infant development.[94] The conclusions were that infant development were similar for term and post-term infants.[95]

In a study by Field et al. post-term infants had a greater head circumference at one year of age compared with controls.[96] This was also observed in a Swedish study, in which

the head circumference was more than 2 SD above the mean for children born at term (14.2% versus 8.8%, p=0.031).[97] However, a large head circumference did not correlate to poor developmental outcome.[97] A multiple logistic regression analysis indicated, however, that the children born post-term had higher risk for developmental deviations than children born at term (13.1% versus 5.5%, OR 2.20; 95% CI 1.29–3.85). The analysis also demonstrated that males generally had more neurodevelopmental disorders than females (OR 1.92; 95% CI 1.11–3.45).[97] Instrumental delivery, SGA and traumatic birth injury did not influence on the odds ratio for developmental deviation.[97]

4.5.4 Maternal outcome

Several studies have reported increased risk of caesarean section and operative vaginal deliveries in post-term deliveries.[88, 98] Operative deliveries and maternal complications are therefore matters of concern in studies of post-term pregnancy management.[22, 30, 89] In a case-control study of Luckas et al., there was an increased risk of caesarean section due to fetal distress (RR 2.0; 95% CI 11.14-3.61) and failure to progress in labour (RR 1.74; 95% CI 1.02-3.04) in post-term deliveries.[88] Long duration of labour and prolonged second stage have also been associated to post-term labours,[29] as well as post-partum haemorrhage.[85, 98] Olesen et al. found an overall maternal complication frequency of 30%, including operative deliveries, post- partum haemorrhage, cervical lacerations, dystocia and puerperal infection.[85] In general, maternal complications are associated with large fetal size, and fetal complications are associated with small fetal size.[6]

4.6 Management protocols

No management protocol for post-term pregnancy is considered to be the gold standard, and management protocols may vary from country to country and from hospital to hospital. There are different suggestions to the questions when follow-up examinations should start, what kind of examinations the follow-up should include, and how frequently the follow-up examinations should be done. Proposed guidelines will be discussed in detail later.

Up to date, there are no examinations with convincing positive or negative predictive values for bad outcome. In an English study, it was concluded that when extensive post-term pregnancy follow-up was done, more interventions were performed without any improvement of pregnancy outcome.[99]

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Studies on efficacy of post-term antenatal surveillance from 41 weeks onwards compared with 42 weeks onwards need to consider pregnancy outcomes, logistic issues and cost-benefit analyses. In a study of Bochner et al. the total number of adverse outcomes in a group of women who started antenatal surveillance at 42 weeks was found to be significantly increased compared with a group starting surveillance at 41 weeks.[100] The authors proposed, however, that a randomised controlled trial was needed to determine the optimal time to start post-term surveillance, and to address the additional manpower, expenses and necessary facilities needed.[100]

4.6.1 CTG

Cardiotocography (CTG) records fetal heart rate, fetal movements and uterine contractions to assess signs of fetal hypoxia. No other examination in obstetrics is more frequently used, but evidence based medical benefits are still lacking.[101, 102] A Cochrane review concluded that there is not enough evidence to evaluate the use of antenatal CTG for fetal assessment.[102] The trials included in the review are old, and the results may be difficult to relate to current practice.[102] Still, CTG is performed as a part of post-term follow-up worldwide.[103, 104] In a survey to all birth units in Norway in 2003, CTG was reported to be a part of the post-term follow-up in all units.[4]

There are no typical FHR patterns in post-term pregnancies. In a case-control study, 2.2% was found to have FHR ≥ 160 and 5.5% had FHR ≤ 120 in the post-term group, but there were no differences in outcome between the term and post-term groups.[105] Computerized analysis of the fetal heart rate has found the variation to decrease with increasing gestational age, and reduced variability is a predictor of intrapartum fetal distress and acidosis in post-term deliveries.[7, 106] Others have found an association between FHR abnormalities and amniotic fluid index (AFI).[107, 108] Divon et al. found an AFI ≤ 5 cm to be a risk factor of FHR decelerations and meconium stained liquor.[108] Further, the frequency of oligohydramnios and abnormal non-stress tests were inversely related to birth weight in the expectantly managed prolonged pregnancy.[109] Maternal ketonuria in post-term pregnancy has been found to be associated with an increased incidence of non-reactive CTG, and a significant increase in FHR decelerations.[110]

During labour, variable decelerations have been observed in up to two-thirds of post-term deliveries, but it has been difficult to differentiate between fetuses in distress and those who experience a normal labour on the basis of variable decelerations alone.[111]

4.6.2 Amniotic fluid

Post-term pregnancy is associated with oligohydramnios. The pathophysiologic mechanism responsible for the development of oligohydramnios has not been established. Estimation of the amount of amniotic fluid is recommended to be a part of post-term pregnancy management protocols.[112] In Norway estimation of the amount of amniotic fluid is part of the post-term follow up in 95% of the birth units.[4]

The amniotic fluid index (AFI) and measurement of the depth of the deepest pocket are both semi-quantitative measures of the amount of amniotic fluid. The AFI is a summary of the largest vertical pocket in each quadrant of the uterus. The pocket should not include an aggregate of cord or fetal extremities. There are divergent views on how the measurements should be performed and what criteria should be used.[113]

AFI and the deepest pocket are usually reported in cm. AFI ≤ 5 cm or deepest pocket ≤ 2 cm is commonly considered indicative for oligohydramnios. Another option to estimate the amount of amniotic fluid is to make a subjective estimate, which is found to be correct in up to 70% of the cases.[114]

Oligohydramnios is associated with fetal heart rate abnormalities and meconium stained liquor.[107, 108] In a study by Alfirevic, five hundred women with singleton, uncomplicated pregnancies with gestational age ≥ 290 days were randomly allocated to fetal monitoring by either AFI and CTG or maximum pool depth and CTG. The proportion of abnormal AFI measurements was significantly higher than the proportion of abnormal maximum pool depths (10% vs 2.4%; OR 4.51; 95% CI 1.82-11.21). This resulted in more inductions for abnormal post-term monitoring in the AFI group, but there were no other statistically significant differences in perinatal or labour outcomes.[115] This is in accordance with another RCT, where the conclusion was that the AFI offered no advantage in detecting adverse outcomes compared with the single deepest pocket.[116] However, some propose that AFI is markedly superior as a predictor of fetal asphyxia before labour.[117] In a UK study, AFI < 5 cm was significantly associated with caesarean section for fetal distress in labour, meconium aspiration, a cord arterial pH <7 at delivery and low Apgar scores.[118] However, both AFI and single deepest pocket are poor diagnostic tests in identifying patients who will undergo caesarean delivery for non-reassuring FHR tracing or deliver a newborn with depression or acidosis.[119]

Maternal hydration for increasing amniotic fluid volume have been suggested to be beneficial in the management of oligohydramnios.[120] This is probably not a good strategy in post-term pregnancies, as induction of labour would be a more appropriate management plan.

In a study of deliveries beyond 41 weeks gestation, AFI > 6 was found to be associated to longer duration of labour and a spontaneous labour was less likely to occur. [121]

4.6.3 Fetal growth

In the past, fetal growth was believed to stop at around 40 weeks with an equalization of the growth curves beyond term.[122] Later studies have demonstrated that fetal growth continues in a steady and linear way until 42 weeks.[123]

Data from the Norwegian Medical Birth Registry indicate that there has been a linear increase in birth weight per year for children born at 40 weeks gestation. The birth weight increase is estimated to be 4 g per year for all births, which corresponds to around 100 g over a 30 year period.[123] In Denmark, the overall mean birth weight increased 45 g, and for infants born at term the increase was 61 g over a ten year period.[124] The risk of having a baby weighing more than 4000 g increased from 17% to 20% in the same period.[124] The proportion of children weighing more than 4500 g at birth was 3.2% in Norway in 1980 and 4.8% in 1999.[125]

Macrosomia is associated with post-term pregnancies. Maternal anxiety and concern are often related to "the big baby" post-term.[69] Still, induction of labour for suspected fetal macrosomia in non-diabetic women does not reduce the risk of maternal or neonatal morbidity.[126, 127] However, one study found increased risk of stillbirth post-term if maternal age was > 40 years and fetal birth weight was moderately increased (2.5-9.9 percentile).[128]

Small fetuses have a high risk for poor obstetric outcome in post-term pregnancies.[6] The incidence of SGA is increased in post-term births compared with term births (3.8% versus 2.2%).[72] Fetal growth restriction has been associated with significantly higher OR for both fetal and neonatal mortality rates at 41-43 weeks. In a study by Divon et al. odds ratios ranged from 7.1 to 10.0 for fetal death and 3.4 to 9.4 for neonatal death.[42] Thus, it is of outmost importance to diagnose fetuses at risk. Ultrasound can diagnose both macrosomia and growth restriction.[129] In one study, ROC-curves (receiver operating characteristic curves) predicted birth weights <10th percentile (3125 g) and <5th percentile (2930 g) in 89% and 96% of cases.[130]

In a Swedish study, a population based standard (adjusted for gestational age and gender) was compared to a customised birth-weight standard (based on the prediction of optimal growth in each individual pregnancy).[131] The customized method was somewhat better to identify fetal growth restriction having an increased risk of adverse perinatal outcome.[131]

Eighty percent of Norwegian birth units estimate fetal weight by ultrasonography as part of their post-term follow-up.[4]

4.6.4 Doppler ultrasound

Doppler ultrasound has no proven benefit in monitoring the post-term fetus and is not recommended as part of post-term management protocols.[132] One Doppler study has indicated that left and right fetal cardiac function was impaired in prolonged pregnancies, and this occurred before the appearance of an abnormal intrapartum FHR.[133] However, in a Swedish study of very prolonged pregnancies (> 43 weeks), there was no association of fetal distress in labour and increased placental vascular resistance.[134] Post-term pregnancies with oligohydramnios did not seem to differ in placental and fetal blood flow distributions from those with a normal amount of amniotic fluid.[135]

4.6.5 Cervix

Information about cervical ripeness is important when induction of labour is considered, and evaluation of the cervix is therefore part of most management protocols. The traditional clinical method for evaluating the cervix is digital palpation and the use of "Bishop score". Recently transvaginal ultrasound has become increasingly popular to measure the cervical length.

4.6.5.1　Bishop score

It is more than 40 years since Edward H. Bishop argued that a standardized evaluation of the cervix was required to determine suitability for elective induction.[136] Five factors are included in the Bishop score: Cervical dilatation, effacement, consistency, position and the station of the presenting part. Each factor is scored on a scale from 0-2, and a Bishop score will range from 0-10. Bishop score > 6 is regarded as a favourable cervix, and ≤ 5 is regarded as unfavourable.

The Bishop score is used worldwide and numerous studies on cervical assessment have been performed. Cervix is rarely found to be favourable in post-term pregnancies. In one

study only 8% was found to have a Bishop score > 6 at ≥ 42 weeks.[137] In a Swedish study of 103 women who were followed from gestational day 294 onwards, 73% of primiparous and 53% of multiparous women had Bishop scores 0-5 at study entry.[87] In this study, primiparous women experienced a more gradual ripening of cervix with increasing gestational length, whereas multiparous women often had a sudden change from unripe to ripe cervix.

The length of the induction to delivery interval is associated with Bishop score, and the likelihood of vaginal delivery within 24 hours has been found to increase with the Bishop score.[138] Further analyses of the different components of the Bishop score demonstrated that only cervical length provided a significant contribution to the prediction of the likelihood of vaginal delivery within 24 hours.[138] In another study, cervical dilatation was found to be more predictive of caesarean delivery than cervical effacement or presenting part station.[139] This contrasts the study of Shin et al., where the fetal station was found to be more predictive for vaginal delivery than dilatation.[140] Others have found dilatation, effacement and station to be better predictive factors to spontaneous onset of labour than consistency and position.[137]

As the Bishop score is a subjective method, the numerical score may vary depending on the examiner. One study demonstrated that if a difference of one point between the observers was found acceptable, the inter-observer agreement was 66%. A formal Bishop score did not improve agreement as compared to an informal global evaluation.[141] By replacing digital assessment of the cervical length by ultrasound measurements, the modified Bishop score was better than the original one in predicting the induction to delivery interval and the success of induction of labour.[142]

Several studies have assessed Bishop score and measurements by transvaginal ultrasound. Some studies find that the methods are comparable,[143-145] some find Bishop score to be best,[146] and others find transvaginal ultrasound to be the best method.[147] Different cut-off values have been used in different studies. In a study of Rozenberg et al., the prediction of labour within 7 days and normal vaginal delivery were similar with a Bishop score 6 or more and an ultrasound measured cervical length of 26 mm or less.[143] In a study by Chandra et al., transvaginal ultrasound did not predict successful labour induction in post-term pregnancy as well as the digital examination did.[146] However, patient discomfort assessed by visual analogue scales demonstrated significantly less discomfort with sonographic assessment of the cervix compared with digital examination.[146]

4.6.5.2   Transvaginal ultrasound

In a Swedish study of 419 nulliparous and 360 parous women cervical length decreased with increasing gestational age beyond 32 weeks in both nulliparous and parous women, but the median cervical length tended to be longer in parous women from 33 to 41 weeks.[148] In a study of Chinese women the mean length of the cervix was shorter throughout pregnancy compared with studies of Caucasians.[149] This may be due to racial differences.

In a UK study, cervical length was measured by transvaginal ultrasound at 37 weeks in 1571 singleton low-risk pregnancies.[150] The median cervical length was 30 mm, and there was a significant association between cervical length and gestational age at delivery.[150] The incidence of delivery after 41+3 weeks increased with increasing cervical length at 37 weeks (0%, 6%, 35% and 68% for cervical lengths of < 20, 21-30, 31-40 and 41-50 mm).[150]

Transvaginal ultrasound measurements of the cervix may be more objective and accurate than Bishop score, because half the cervix is not palpable at digital vaginal examination when the cervical canal is closed. In one study sonographically measured cervical length was found to predict the outcome of induction better than the Bishop score or cervical length by vaginal examination.[147] ROC curves (receiver–operating characteristics) demonstrated that ultrasound was better than Bishop score in the prediction of all caesarean sections (72% versus 68%) and caesarean sections for failure to progress (76% versus 69%).[151] This is in accordance with a study by Gabriel et al., which concluded that for women with unfavourable Bishop score, a cervical length of < 26 mm was associated with a lower risk of caesarean section and a shorter duration of labour.[152]

It is important to be able to predict failure of induction of labour. One study indicated that transvaginal ultrasound of the cervix was better than the Bishop score to predict a successful labour induction.[153] If the cervix measured 32 mm or more, 85% of women remained undelivered after 24 hours compared to 65% undelivered if the Bishop score was two or less.[153] However, study results are contradictory. Another study concluded that ultrasound did not improve the prediction of cervical inducibility obtained by the Bishop score.[154] In nulliparous post-term women the use of a logistic regression model including both Bishop score and sonographic cervical length was more likely to predict the onset of labour within 24 hours than the use of Bishop score alone or ultrasound alone.[155] In a Norwegian study, the mean distance from the outer bony part of the fetal skull to the skin of the perineum (fetal head–perineal distance) was measured by transvaginal ultrasound in women with prelabour rupture of membranes at term. Women with a short fetal head–perineal distance (<

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45 mm) had statistically significant shorter time from rupture of membranes to start of labour, and a shorter time from induction to delivery.[156]

Recent studies have suggested that 3D ultrasound examinations of the cervix allow a more complete assessment of the cervix than the 2-dimensional (2D) ultrasound approach. However, the results of 3D power Doppler ultrasound examinations before induction did not predict outcomes of labour induction in post-term women.[157] In prolonged pregnancy, cervical vascularisation (estimated by 3-dimensional power Doppler ultrasound) was related to time to delivery >48 hours. However, the likelihood of delivery >48 hours can be predicted equally well using Bishop score alone or sonographic cervical length alone.[158]

4.6.5.3   Fibronectin

Measurements of fetal fibronectin in vagina or cervix have been introduced as screening methods to predict preterm labour. A high fetal fibronectin level is associated with delivery within the near future.[159, 160] However, the use of fibronectin test has never been a well-established part of post-term follow-up.[161]

In a retrospective study, fibronectin was measured in gestational week 39-40, and the presence of vaginal fibronectin concentration <60 ng/ml identified 96% of women who delivered beyond 41 weeks.[162] For those who delivered before 41 weeks, a 35 fold increase in fibronection concentration was found.[162] This contrasts the results of a Swedish study in which the concentration of fetal fibronectin in vaginal fluid was elevated in only 36 of the 80 post-term women, and a positive fibronectin concentration had no correlation with delivery in two or three days.[163] Mouw et al. have also concluded that fibronectin test can not predict whether birth will take place within three days or not.[164]

4.6.5.4   Insulin-like growth factor binding protein-1 (IGFBP-1)

The detection of amniotic fluid isoforms of IGFBP-1 in cervical and vaginal samples is diagnostic for the rupture of fetal membranes.[165] Phosphorylated isoforms of IGFBP-1, different from those found in amniotic fluid, are present in the cervical secretion of women with intact fetal membranes and reflect cervical ripeness.[165] Nuutila et al. have suggested that a bedside test for phosphorylated IGFBP-1 isoforms might help to predict suitability for labour induction.[165] Studies on IGFBP-1 and cervical ripeness in post-term pregnancies are lacking.

4.7 Induction of labour

Induction of labour has been associated with labour complications and in particular with increased risk of caesarean section.[166, 167] Labour induction was associated with an increased caesarean delivery rate from 13.7% to 24.7% (OR 1.70; 95% CI 1.48-1.95) in primiparous women, and from 2.4% to 4.5% (OR 1.49; 95% CI 1.10-2.00) in parous women.[168]

Post-term pregnancy is a common clinical indication for labour induction. In the United States induction of labour is one of the most frequently performed medical procedures, and the proportions of induced labours increased from 9% in 1989 to 19% in 1998.[169] The gestational age distribution curve for induced births has showed a marked shift to the left, and the proportion of all induced births occurring post-term fell from19% to 9% during the same time period, whereas term induction increased from 73% to 83%.[169] This change has not been observed in Norway. The proportion of induced labours in Norway has increased over the last years, but the proportion of induced labours are still relatively low (12% in 2002, according to data from the Norwegian Medical Birth Registry). The proportions of induced labours post-term are in accordance with the results from the survey to Norwegian birth units (Table 2).

Table 2. Induced labours beyond 41 weeks gestation in 2003 according to statistics from the Norwegian Medical Birth Registry.

Gestational age, days	Number of births	Number of induced labours	Proportion of induced labours, %
287	1 843	157	9
288	1 712	162	10
289	1 612	165	10
290	1 448	168	12
291	1 322	175	13
292	1 191	178	15
293	993	176	18
294	931	166	18
295	805	220	27
296	811	357	44
297	730	404	55
298	426	249	59
299	257	168	65
300	119	73	61

4.7.1 Methods

There are numerous different methods for induction of labour, which is reflected in 24 different Cochrane reviews on the topic. In a survey to all birth units in Norway in 2003, about 50% of the units used dinoprostone gel for induction of labour and 25% used misoprostol.[4] There were a total of 24 different administration and dosage regimens in use.[4] Only a few methods will be discussed here, primarily the methods recommended in the Norwegian Guidelines for Obstetrics.[170]

A number of "old wives" tales are still used by many women to encourage start of labour. Among the more common approaches are frequent walking, vaginal intercourse, participating in heavy exercise, consumption of laxatives, spicy foods or herbal tea, nipple stimulation and administration of an enema.[171] There has been some research on these

methods, and even a few Cochrane reviews exist, but the research is inconclusive, and there is usually no evidence of effect.[172-175]

Studies usually compare efficacy of labour induction methods stratified into whether cervix is favourable or unfavourable, although cervical ripening is a continuum. When cervix is unfavourable, prostaglandins are usually the preferred method for cervical ripening. Prostaglandins have been used for induction of labour since the 1960s, and many studies have been reported since then. From the early 1990s, the synthetic prostaglandin analogue misoprostol has been used and appears to be at least as effective as more conventional prostaglandins.[176, 177]

The results on effect and side-effects of prostaglandins are conflicting. Both prostaglandin E_2 and F_{2a} are found to increase successful vaginal delivery rates within 24 hours without increasing operative delivery rates.[178] However, uterine hyperstimulation with or without FHR changes have been associated to the use of prostaglandins and related to the dosage.[177, 178] The definition of uterine hyperstimulation varies. In one study hyperstimulation was defined as tachysystole (> 5 contractions per 10 minutes for at least 20 minutes) or hypersystole (contractions lasting at least 2 minutes),[177] while others defined hyperstimulation as tachysystole with fetal heart rate changes.[179] A systematic review of studies on misoprostol compared with prostaglandin E_2 for labour induction at term, (with intact membranes and unfavourable cervix) demonstrated no difference in the risk of caesarean delivery. However, the use of misoprostol was associated with a higher risk of tachysystole (RR 1.86; 95% CI 1.01-3.43) and hyperstimulation (RR 3.71; 95% CI 2.00-6.88).[179] The optimal method of induction of labour, including route of administration and dosage, is still under debate.

When cervix is favourable, the recommended methods are sweeping of the membranes, amniotomy and/or oxytocin. Amniotomy and membrane sweep are frequently requested by women wanting a drug-free labour. The available evidence suggest that membrane sweep promote the onset of labour.[180] In one study, membrane sweeps increased the spontaneous vaginal delivery rate, shortened induction to delivery interval, and improved patient satisfaction.[181] In a RCT of low-risk pregnancies at 41 weeks, serial sweeping of the membranes decreased the risk of post-term pregnancy (RR 0.57; 95% CI 0.46-0.71, NNT 6).[182]

Oxytocin is the most frequently used induction agent worldwide. It may be used alone, in combination with amniotomy or following cervical ripening with other pharmacological or non-pharmacological methods.[183] A Cochrane-review included 40 trials and 5893 women, and found that using PGE_2 rather than oxytocin was probably more effective to induce labour.[183] It

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is noteworthy that there was no increase in uterine hyperstimulation with fetal heart rate changes in any of the comparisons. This contrasts the common belief that the use of oxytocin is associated with fetal distress and adverse outcome.[183, 184] The combination of amniotomy and intravenous oxytocin have been widely used in obstetric practice, but surprisingly little research have been done. Meta-analyses do not clearly support or refute the value of using a combination rather than separate methods individually, and no recommendations for clinical practice have been made.[185] A review of trials in the Cochrane database did not find evidence to support the use of amniotomy alone for induction of labour.[186]

4.7.2 Economical considerations

Cost is a major issue when recommendations about induction of labour are considered. Obviously the costs of induction include far more than the price of the medications used. Induced labours are "high risk labours", and additional monitoring is required. According to a Canadian study, the costs of delivery after induction of labour was increased compared to spontaneous onset of labours ($1715 versus $1474, P<0.001).[187] In a theoretical study, induction of labour at gestational age 40, 41 and 42 required expenditures from the medical system regardless of parity and cervical ripeness, and induction of labour was never cost saving.[188] However, for parous women and for women with a favourable cervix, inductions were less expensive at later gestational ages.[188]

Post-term pregnancies managed expectantly will also need extra operating expenses and resources in terms of follow-up examinations with CTG and ultrasound. Cost-minimization analyses were conducted as part of the Canadian Multicenter Post-term Pregnancy Trial, and the mean costs per woman were found to be $ 3132 for a pregnancy managed expectantly and $ 2939 per patient who underwent induction of labour (p<0.0001).[189]

5   Basis for the study

Obstetricians are always alert when a post-term woman is in labour at the delivery unit. The fact that there are different guidelines regarding post-term pregnancy management around the world, and a general feeling that there is no gold standard for medical treatment, we found it important to undertake new studies.

In Scandinavia there has been a conservative approach to post-term pregnancy management.[87, 98, 103, 104, 190] Most obstetricians in Norway follow the National Guidelines and await follow-up until 42 weeks. Swedish obstetricians have a similar approach. In a survey, 87% of Swedish delivery units said that they would await spontaneous delivery in normal pregnancies until 42 weeks of gestation, and only 9% would induce labour at 41 weeks.[42] Antenatal surveillance was initiated at 41 weeks by 5% and at 42 weeks by 95% of the units.[42] The standard management of prolonged pregnancy in Finland has been antenatal surveillance from 41 to 42 weeks of gestation, and induction of labour at 42 weeks if the cervix is favourable.[98]

A meta-analysis on post-term pregnancy management has, however, recommended induction of labour after 41 weeks to reduce the risk of perinatal death. In the meta-analysis, routine induction of labour was not associated with an increased risk of caesarean section, regardless of parity, state of the cervix or method of induction, and there was no increase in instrumental delivery rate, use of analgesia or incidence of fetal heart rate abnormality.[22] As a consequence, many countries changed their guidelines.[112, 191]

However, this meta-analysis has created some discussion in the scientific community.[103, 192] The major objections put forward have been that some fairly old studies were included, and that the Canadian Multicenter Post-term Pregnancy Trial strongly influenced the meta-analysis due to the sample size of the trial. This trial is not without criticism from obstetricians worldwide.[87, 103, 192, 193]

The Canadian Multicenter Post-term Pregnancy Trial included 3407 women from 22 hospitals. The aim of the trial was to determine the effect of routine induction of labour at 41 weeks on perinatal mortality and neonatal morbidity as compared with a policy of expectant management with serial antenatal monitoring.[30] A secondary objective of the trial was to determine if induction of labour resulted in increased or decreased rates of caesarean delivery.[30] The study reported no differences in perinatal mortality or neonatal morbidity between the randomised groups, and induction of labour resulted in a decreased rate of caesarean delivery compared with serial antenatal monitoring (21.2% versus 24.5%, p=0.03).[30] One important criticism towards the study was that different methods for estimating gestational age were used in the trial and that different methods for induction of labour were used in the randomised groups.[87, 192] In the induction group cervix was ripened with prostaglandin gel, whereas labour was induced by oxytocin or amniotomy in the monitored group. The operative delivery rate was more than 50% in both trial arms, and it has been argued that the results might not be valid in West-European countries.[87]

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The guidelines from the Royal College of Obstetricians and Gynecologists (RCOG) conclude that ultrasound should be offered before 20 weeks gestation to confirm gestational age, and that women with uncomplicated pregnancies should be offered induction of labour after 41 weeks.[112] The ACOG Practice Bulletin (American College of Obstetricians and Gynecologists) is less conclusive, and suggests that women with post-term pregnancies who have unfavourable cervices can either undergo labour induction or be managed expectantly.[132] A questionnaire was mailed to 1000 randomly selected ACOG Fellows and Junior Fellows to investigate attitudes and practice patterns toward post-term pregnancy. Post-term pregnancy is defined by ACOG as 42 weeks of gestation or more, but only 48% of the practicing obstetricians in the study defined post-term pregnancy as 42 weeks gestation or more.[194] In all, 73% reported that they routinely induced low-risk patients with singletons at 41 weeks gestation.[194]

The meta-analysis on post-term pregnancy concluded that there was no need for further randomised trials of routine induction of labour versus conservative management.[22] However, a Swedish "State of the Art- management of post-term pregnancy" conference came to the opposite conclusion, recommending that a Scandinavian randomised trial should be done.[87] A recently published study from Finland also concluded that there is an urgent need for a prospective randomised study on management of post-term pregnancies.[98]

6   Aims of the studies

6.1 Study 1

The aim of the study was to evaluate pregnancy complications and perinatal outcome for pregnancies at or beyond term when onset of labours were spontaneous or induced.

6.2 Study 2

The aim of the randomised controlled trial was to compare induction of labour at gestational age 289 days (41 weeks + 2 days) with expectant management with respect to neonatal morbidity. A secondary aim was to assess the effect of induction of labour and expectant management on the mode of delivery and maternal complications.

6.3 Study 3

The aim of the survey was to explore women's preferences of post-term pregnancy management. We also wanted to study women's experiences after participation in a clinical trial of routine antenatal fetal monitoring or induction of labour.

6.4 Study 4

The aim of this study was to assess risk estimates for fetal and perinatal deaths day by day beyond 41 completed weeks in a Norwegian population, and to estimate numbers needed to induce to avoid one fetal or perinatal death.

7 Subjects and methods

The study population in Study 1-3 came from a geographically well-defined area consisting of the city of Trondheim and eight surrounding municipalities. This area is served solely by St. Olavs Hospital, Trondheim University Hospital for all obstetric and perinatal care. In this non-selected population, 98 % of all pregnant women have a routine ultrasound scan at around 18 weeks and delivery at St. Olavs Hospital.

7.1 Study 1

Demographic characteristics, obstetrical history and data from all ultrasound scans were prospectively recorded in a computerized database. After delivery, additional data from the delivery and all neonatal outcomes were included in the database.

Women were included if they had a singleton pregnancy with reliable dates and delivery beyond 37 weeks of gestation. The methods for induction of labour were amniotomy/oxytocin if cervix was favourable, and prostaglandin E_2 when cervix was unfavourable. Post-term follow-up was initiated 14 days after the estimated date of delivery. If the pregnancy was uncomplicated, the woman attended follow-up examinations every second day until spontaneous delivery occurred or labour was induced at 43 completed weeks.

7.2 Study 2 and 3

Women were informed about the study when they attended the routine ultrasound scan at around 18 weeks. They were invited to book appointments at 41 weeks gestation. Eligible

women received a reminder phone call around 41 weeks if no follow-up appointment had been made.

All women had the same baseline assessment and answered the questionnaires on attitudes to post-term pregnancy at the time of inclusion. The methods used for induction of labour were amniotomy/oxytocin when cervix was favourable, and misoprostol when cervix was unfavourable (dinoprostone when the uterus was scarred).

Neonatal morbidity is a multifactorial outcome, and we chose to report commonly used and self-explanatory outcomes such as Apgar score, pH, Base excess, excessive birth weight, presence of infection or hypoglycaemia. In addition, we decided to report cut-off values for variables commonly considered to represent bad obstetric outcome (umbilical cord pH <7.10 or 7.00 or Base excess <12). A neonatal morbidity score (NEMO-score) was established for this study in order to compare groups quantitatively. NEMO score is a sum of deviations from the optimal neonatal outcome. We defined a perfect outcome as being an infant with a birth weight of 3.8 kg and a Ponderal Index of 2.88. Other optimal features for outcome were considered to be 1- and 5-minute Apgar scores of 10, umbilical cord pH 7.40 with base excess equal to 0 (zero), and no medical complications or need for treatment. To compare the study groups quantitatively we assigned a priori weights to the outcome variables, based on clinical judgment and consensus among the researchers. The sum in each neonate constitutes a Neonatal Morbidity score, which increases with increasing morbidity.

A telephone survey 6-8 months post partum was performed by the principal author (78% of interviews) and one secretary (22% of interviews). The questionnaire on attitudes and preferences of management was established in cooperation with midwives, colleagues and patients, and the questionnaire was tested in a pilot study.

7.3 Study 4

The data source for this study was the Medical Birth Registry of Norway. The present analysis was based on an anonymous extraction file from all singleton births from 1999-2005. Births with gestational age < 287 days and > 315 days were excluded from the analyses, as were births with unknown gestational age. Fetal malformations were excluded from the study.

7.4 Statistics

7.4.1 Statistical analyses

In study 1, Pearson Chi-Square was used to test for differences in the crude analysis of perinatal outcomes and pregnancy complications. To assess linear associations across gestational weeks, we used the Chi-Square test for trend for proportions and linear regression for continuous variables. We performed a multivariable logistic regression analysis to control for possible confounders such as gender, smoking, maternal age, parity, and birth weight. The relative risks of complications were estimated and expressed as odds ratios (OR) with 95% confidence intervals (CI).

In study 2, groups were compared according to the intention to treat principle. Student's t-test was employed for continuous variables. Mann-Whitney test was used for ordinal variables and Fisher's exact tests with mid-p values for 2-by-2 tables.

In study 3, the Wilcoxon signed rank-test for paired observations was used to compare mean scores at inclusion and postpartum. Continuous variables are presented as means with standard deviations (SD), ordinal variables as medians with range, and categorical variables as numbers and percentages. Two-tailed tests were employed throughout the analyses, and a p-value < 0.05 was considered statistically significant.

In Study 4, differences in death rates and in numbers needed to treat were evaluated using proportion comparisons tests, and 95% CI for proportions were estimated using the exact option in the program package STATA.

7.4.2 Sample size estimation

Sample size estimation is not relevant in population based epidemiological studies (study 1 and 4).

The randomised controlled trial had set a time frame of about two years, which made it realistic to enrol about 500 women. This sample size was considered acceptable in light of the results from two (unpublished) pilot studies, a retrospective study with n=20 and a prospective study with n=29. The pilot studies were undertaken prior to the trial to evaluate the feasibility of the NEMO score. Both pilot studies found a mean difference of about 1.5 (with SD ≈ 4) on the NEMO scale in favour of induction, and we found this difference to be clinically relevant. It corresponds to a standardized difference (mean difference /SD) of 0.38.

To detect a standardized difference of 0.3 with a power of 80% at a two-sided significance level of 5% we would need 176 subjects in each group. The final sample size of 254 in each group enabled a detection of a standardized difference of 0.25 (i.e. approximately 1.0 on the NEMO scale), and an absolute difference of 10% regarding operative deliveries.[195]

8   Main results

8.1 Study 1

In this epidemiological study we found that poor pregnancy outcomes varied with gestational age and onset of labour. Both post-term pregnancy and induced labour were prognostic factors for poor obstetric and neonatal outcome.

The caesarean delivery rate was stable around 12%, and the overall proportion of operative vaginal deliveries was constant around 8%. Maternal complications varied with gestational age, and were lowest at 39 weeks and highest post-term (caesarean delivery 12.3–21.6%, operative vaginal delivery 10.7–15.4%, maternal haemorrhage 9.7–14.6%). Poor neonatal outcome varied with gestational age only for spontaneous labours (Apgar < 7 at 5 minutes; 1.0–2.3%, pH < 7.10; 3.4 –5.2%).

Induction of labour was a risk factor for delivery complications (OR 1.3–2.8), independent of gestational weeks, as were maternal age >35 years and nulliparity.

8.2 Study 2

In this randomised controlled trial we found no differences in neonatal morbidity or delivery complications between the groups. Neonatal outcome was generally good, and there were no differences in the proportions of NICU admissions, Apgar scores or umbilical blood pH. When all outcome measures in the scoring systems developed for post-term morbidity (the NEMO score and the score used in the Canadian Multicenter Post-term Pregnancy trial) were assessed, we found no differences between groups. However, there was a trend towards more frequently observed meconium-stained amniotic fluid during labour in the monitoring group (p=0.08), and the neonates were 0.4 cm longer (p<0.01) and tended to have higher birth weights (p=0.09).

There was no difference in the caesarean delivery rate between the groups. Precipitate labours and short active second stage labours occurred more frequently in the induced group. In the monitoring group, an active second stage > 60 minutes was more frequently seen.

8.3 *Study 3*

At 41 weeks the majority of women (73%) preferred immediate induction, despite the fact that 40% of them believed that the complication rate would increase if labour was induced. After delivery, four of five women in the induction group said they would be keen to follow the same management pathway in a future pregnancy. Only two of five women who had serial antenatal monitoring would prefer this option again. In the monitored group the proportion of women who thought induction at 41 weeks should be mandatory was larger when they were asked 6-8 months after delivery. This change in attitude was not observed in the induction group. The majority of women (84%) reported a positive labour induction experience.

8.4 *Study 4*

The perinatal death rate increased with increasing gestational age (0.18‰ at day 288 to 5.1‰ at day 302+, p<0.001). NNTs (inductions necessary to avoid one IUFD or perinatal death) decreased with increasing gestational age (p<0.004). NNT for IUFD was 671 at day 287 and 195 at day 302+. NNT for perinatal death was 527 at day 287 and 195 at day 302+.

9 Discussion and interpretation of the results

Study 1 was an observational study of the medical consequences of gestational age and induction of labour in a Norwegian population. We observed that both post-term pregnancy and induction of labour were independent risk factors for poor outcome. We acknowledged that only a randomised controlled trial could bring further information on this topic.

The most recent Norwegian randomised controlled trial on post-term pregnancy was published 20 years ago.[196] The study was well designed and was included in a Cochrane review of 18 studies on post-term pregnancy management.[83] Augensen et al. found no differences between the groups in the trial, and the authors concluded that either type of management (induction at 42 or 43 weeks) appeared to be safe. However, this trial was performed before prostaglandins were introduced for labour induction. This may explain the

high proportion of failed inductions (23%) in the trial. Furthermore, this trial was performed before ultrasound was generally available. A large proportion of women (57%) were excluded from the trial, mostly because of unreliable dates. Compared to today, the caesarean delivery rate was rather low (7-8%). However, the operative vaginal delivery rate was around 10%, and this is comparable to our trial. The results from the two Norwegian studies done 20 years apart were quite similar, but induction of labour was done a few days earlier in the most recent trial. It is noteworthy, however, that the clinical conclusions and recommendations from the two trials differ. Augensen et al. proposed that induction of labour should be postponed due to the minimal risk of expectant management. We argue for the opposite conclusion due to several reasons, but primarily due to the increasing perinatal mortality rate post-term. This was demonstrated in Study 1 and 4, and has also been found in many other studies. [22, 28, 75, 83] Further, the majority of women prefer induction of labour rather than antenatal fetal surveillance.

For years obstetricians have been convinced that induction of labour cause maternal and neonatal complications. The results in Study 1 support this theory. In 1998 the Norwegian Medical Association carried out a "Break Through project on caesarean section" to try to reduce the increasing rate of caesarean deliveries. All labour units in Norway were invited to participate. Most participating units focused on a reduction in inductions as a possible way to reduce the caesarean delivery rate. Failed labour induction is a very negative experience for both mothers and obstetricians, and may be a contributing factor to their suggestion to postpone inductions. In Study 2 the rate of failed induction was rather low (6/293).

A Cochrane review was available when Study 2 was planned. The review concluded that no further randomised controlled trials of routine induction of labour versus conservative management were needed.[22] Thus, it may be argued that it was unnecessary, and perhaps even unethical, to go through with our trial. Lots of money and manpower are needed to conduct a randomised controlled trial, and patients have to spend time for examinations they otherwise would not have. On the other hand, Scandinavian management protocols of post-term pregnancy had not changed according to the conclusions from the Canadian Multicenter Post-term Pregnancy trial or Cochrane, and there was a request for a new trial from Scandinavia.[87] The Scandinavian countries may be different from other countries for several reasons. The population is homogeneous, the operative delivery rates are low and the health care system is free of charge. Almost all women attend pregnancy care.

In Study 2 the pregnancy surveillance was done according to Scandinavian recommendations, and the operative delivery rates were comparable to rates from other

Scandinavian countries. Thus, the results of the present trial may have an impact on Scandinavian practice. We anticipate that Scandinavian post-term pregnancy management protocols will become more in line with evidenced based medicine in the future.[83, 112]

In the most recent Cochrane review from 2006, it is concluded that it would be useful to conduct research to obtain women's views about management options.[83] This was addressed in Study 3. At a post-term follow-up, a pregnant woman should be informed about a small but increased risk of stillbirth and perinatal death if she continues the pregnancy beyond 41 weeks. She should also be told that there is no difference in neonatal morbidity or caesarean delivery rate if she chooses expectant management or induction of labour. Expectant management is a legitimate option provided appropriate monitoring of pregnancy. Furthermore, she should be informed that most women report a positive experience with induction of labour, and that women who have been expectantly managed prefer induction of labour in a future pregnancy. However, the delivery may be somewhat more precipitate, and contractions may be more intense if labour is induced. This may be due to the misoprostol dosage regimen used in the most recent trial, and a lower dose of misoprostol may influence the women's experience on this matter.

It is reasonable to believe that an even greater proportion of women would have a positive experience with induction of labour if the contractions were less intense. We have recently changed our dosage regimen for induction of labour at St. Olavs Hospital. The new low dose regimen is in line with the recommendations in the clinical guidelines from the Norwegian Society of Obstetrics and Gynecology,[170] and these guidelines are in accordance with international recommendations.[197] However, the use of low-dose regimens may be difficult and impracticable because the drug is currently only available in 100–200 μg tablets. The use of 25 μg requires multiple cutting of the tablet, involving a risk of inaccurate dosage. One previous study found that 42–74% of approximated one-quarter tablets (one-quarter of a 100-microgram tablet) failed to provide misoprostol dose within 10% of the desired dose.[198]

The methods for cervical ripening were different in Study 1 and Study 2. This may influence the comparison of the results, especially regarding outcomes of labour. In Study 1 dinoprostone was used. This has been reported to be less effective compared with misopostol.[153] In Study 2 the routine method for induction was misoprostol, and this was used in 239 women. In line with the study protocol, dinoprostone was used in 19 women with a scarred uterus. We believe that the larger proportion of prolonged first and second stages of labour found among induced labours in Study 1, but not in Study 2, may be related to the induction method.

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There are reports of ruptured uterus after use of dinoprostone as well as misoprostol.[179, 199] In a recent review article there were no differences in adverse maternal outcomes for misoprostol or prostaglandin E_2 use.[179] It has been stated that both elective caesarean section and induction of labour are reasonable choices for women with previous caesarean section.[200] Others argue that women who undergo trial of labour after the estimated date of delivery have a significantly increased risk for scar rupture.[201]

The precautions taken towards induction of women with scarred uterus are mostly of medico legal character. Misoprostol is not approved for the induction of labour, and any misoprostol use among pregnant women must be considered to be "off-label" use of the drug. This "off-label" use has raised an important discussion between the manufacturer, governments and obstetricians worldwide.[202-204] Misoprostol is cheap, thermostable (may be stored in room temperature), efficient and safe. However, the manufacturer does not want to apply for official use because they will not make much money, and they might face future litigations. Still, misoprostol is one of the most important medications in obstetrical practice. More than 200 studies involving more than 16 000 women have evaluated its effectiveness in pregnant women, and the results support its continued use.[203]

As far as we know, there is only one previously published randomised controlled trial on post-term pregnancy management using misoprostol.[205] The methods in the study by Gelisen et al. were somewhat different, and the results may be difficult to compare. The induction group in their study had three treatments arms: Vaginal administration of 50 µg misoprostol (n = 100), oxytocin induction (n =100) or transcervical insertion of a Foley catheter balloon (n = 100). Membrane sweeping were done in all groups before induction. In the study by Gelisen, induction of labour was scheduled in the monitored group at 294 days, in our study at 300 days. They reported that birth weight > 4000 g, shoulder dystocia, meconium-stained amniotic fluid, and meconium aspiration syndrome were significantly more frequently occurring in the follow-up group. Their findings on birth weight were in line with our results, but we could not demonstrate statistically significant differences in any other outcomes.

The proportion of self-reported smoking during pregnancy was different in Study 1 and Study 2. In Study 1, 21% were smoking during pregnancy, but this proportion had dropped to 11-12% in study 2. Several factors may contribute to this difference. Pregnant women have quitted smoking quite dramatically in recent years. In 1987, Norway was on the top of the world list of smoking during pregnancy (35-40%) and in 1995 this proportion was

reduced to 20%.[206] The proportion of smokers in our well defined population was 27% between 1987-1992.[207]

Smokers have reduced risk to deliver post-term.[48] Study 1 included women from 37-43 weeks of gestation, but the information about smoking habits was given when they attended routine ultrasound at around 18 weeks. In Study 2 they were asked about their smoking habits at 41 weeks. Some women may quit smoking during pregnancy.

A limitation of our trial was that one third of the monitored women were induced because of medical indication. Induction for medical reasons was associated with increased intervention rates. The label of a "high-risk" pregnancy may have influenced the obstetrical decision making. The recognition of risk factors such as meconium-stained liquor resulted in the use of continuously electronic fetal monitoring rather than intermittent auscultation, and this may also have influenced intervention rates.[208] We did not record the frequency of tachysystole or hyperstimulation, but we found no increase in nonreassuring fetal status in the induction group.

It may be argued that stratification for parity should have been done in the trial, since nulliparous and parous women have different labour courses. We decided not to carry out a stratified allocation in the trial because we assumed that the process of randomisation would give a balanced distribution of nulliparous and parous women between study groups. Any subgroup analysis should be done with caution, and the trial was not powered to look at any subgroups. Thus, subgroup analyses were not done.

The introduction of a new score (NEMO score) to measure neonatal morbidity is debatable. Neonatal morbidity is a multifaceted phenomenon, and we chose to report commonly used and self-explanatory outcomes such as Apgar score, pH, base excess, excessive birth weight, presence of infection, hypoglycaemia etc. because neonatal morbidity was the primary outcome of the study. In addition, we reported statistics on cut-off values for variables commonly considered to represent poor obstetric outcome (umbilical cord pH <7.10 or 7.00 or base excess <12). However, we believe that a summarized score of morbidity is more clinical interesting than individual variables. This is also agreed by Caughey et al.[92]

If a universally accepted morbidity score had been available, we would have used it in the trial. However, most published neonatal scoring systems focus on preterm neonates admitted to NICU and/or address neonatal mortality. In our trial neonates were post-term, only a small group of children were admitted to the NICU, and mortality was therefore not the focus of our study. Thus, we found previous scores unsuitable for our purpose.

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The proposed NEMO score is a sum of deviations from the optimal neonatal outcome. The weighting of the different variables may be debated, but they are transparent, and the scale itself may be interpreted from its components. Furthermore, the randomised design ensures that group comparison should be valid.

In addition we applied the score developed by Hannah et al. on our dataset.[30] An adjudication of the definition in the CMPP- trial was made after the first 1500 infants were born, and a consensus conference was held to define further the measures of neonatal morbidity.[30] This fact illustrates the complexity of the morbidity definition problem. In fact, Mary Hannah herself advised us not to use the CMPP-trial scoring system, and said "*it was completely useless* "(personal communication). We chose to report it anyway because we found it important to compare our results with the influential CMPP-trial. We do not know for sure that our score (NEMO score) is clinically more useful. Hannah et al. were unable to demonstrate any differences in morbidity with her scoring system in a study with 3400 women. It was probably too optimistic to believe that we could demonstrate any statistically significant difference in a study with 500 women, although power calculations based on pilot studies indicated that this could be possible. On the other hand, if it is impossible to demonstrate any statistical difference in a randomised trial with 500 women, one might argue that there is hardly any difference of clinical importance between the groups.

Not all data from Study 2 and 3 have been analysed, and we aim to study one or more of the following topics:

- Hormones in post-term pregnancy
- Cervical changes in post-term pregnancy
- Amniotic fluid measurements
- IGFBP-1, cervical ripening and time to delivery
- Smoking – second trimester, post-term and post partum

10 Conclusions

In Study 1 we found that both post-term pregnancy and induction of labour were prognostic factors for poor outcome. In Study 2 we found no differences between neonatal morbidity and mode of delivery for post-term pregnancies managed expectantly with serial antenatal surveillance or by immediate induction of labour. The outcomes were generally good. In Study 3 we found that the majority of women preferred induction of labour, and their

experiences with labour induction were good. There was a significant decrease in NNTs to avoid IUFD and perinatal death from 41 weeks to 43 weeks, but the NNTs were quite high. We suggest that induction of labour should be offered at 41 weeks of gestation. However, expectant management is a legitimate option provided appropriate monitoring of pregnancy.

11 Final reflections and future aspects

In the following section I will share my thoughts and vision for the future. Some thoughts are based on evidence, others are more speculative.

There has been a shift in obstetric management during the last decade, and the proportion of induced labours is increasing worldwide. In a study from Minnesota, the increase in the induction rate for gestational age 37-41 was 130% between 1989 and 1998.[169] The gestational age distribution curve for induced births showed a marked shift to the left during the same period.[169] The mean gestational age associated with inductions in post-term pregnancies decreased from an average of 41.9 weeks in 1980 to 41.0 weeks in 1995 (p=0.001). In 1980 19% of all term deliveries were ≥42 weeks' gestation and in 1995 this proportion had decreased to 2% (p=0.001).[209] One of the largest overall increases in inductions was found to be in inductions labelled as elective.[209] Caesarean on request and elective inductions both reflect the improved ability and wish to plan the timing of delivery. It has been proposed that women in the 21st century will claim their rights to choose how, where and by whom they should be delivered.[210] Modern women are used to plan their lives in detail, and schedule every hour of the day. Delivery is one of few unpredictable things in life. Many women find it unpleasant and fearful not to know when the labour starts, how painful it will be, how long it will last etc. One of the elements of uncertainty can be eliminated by induction of labour. Elective inductions will probably increase in the years to come.

In Study 2 we demonstrated that the outcomes were generally good when labour was induced at 41 weeks, and in Study 3 we found that induction was preferred by most women. In Study 1 we demonstrated that the risk of complications generally was at the lowest at gestational week 38-39. If the trend to induce at earlier gestational ages continues, one future RCT should compare labour induction at 39 weeks and 41 weeks.

Study 1 demonstrated that the complications at 39 weeks were low, but also that induction of labour was a risk factor for bad obstetric outcome. In a small randomised

controlled trial from Japan (N=194), labour was electively induced at 39 weeks or expectantly managed to 42 weeks.[211] In this trial, there was an increased incidence of meconium stained amniotic fluid and need for fetal resuscitation in the expectant group, but no statistical significant differences in neonatal outcome or caesarean delivery rate.[211]

A policy of early induction will implicate an enormous increase in the number of inductions, and medical consequences as well as logistic consequenses have to be considered. It is difficult to do cost-benefit analyses of induction of labours. According to a Canadian study, the cost of delivery after induction of labour was increased compared to spontaneous onset of labour.[212] However, it is an interesting suggestion to be able to manage a great majority of deliveries. Perhaps a future obstetric department could be run mainly during daytime, where induction of labours and elective caesarean sections are scheduled. This might be cost saving, since human hospital resources could be used during daytime instead of week-ends and nights. Obstetrics is the hallmark of emergency, and the activity and workload are the same 24 hours a day. A reduction of night-shifts among obstetricians and midwives may recruit young people to choose obstetrics. In our brand new department at St.Olavs Hospital, there are two identical delivery units. There are numerous delivery rooms, but there is a lack of staff and economy to operate two separate units 24 hours. A consequence analysis of a strategy of two department open during day-time and one in the evening/nights would be interesting. It is of course impossible to schedule every single delivery, and flexible working shifts will be necessary. However, the induction to delivery time may to some extent be estimated from parity and cervical ripening, and one delivery unit could be run on a 8-5 basis.

To follow this chain of thoughts further, one might imagine that the majority of women can have their labour induced on an out-patient basis. This may be a reasonable option for several reasons. One study demonstrated that a latency of approximately 15 hours after a single low dose of misoprostol can provide induction benefit and may minimize the problem of uterine tachysystole/hyperstimulation associated with repeated dosing.[213] A single dose of misoprostol was more effective than a single dose of prostaglandin gel for out-patient labour induction.[213] No differences in adverse outcomes were found between inpatient or outpatient induction of labour.[214] However, the women in the outpatient group reported significantly more satisfaction than the inpatient women.[214] In addition, the need of hospital resources will probably be reduced by an out-patient induction policy.

Risk assessment has become popular in modern medicine. To help women to decide whether to have their labour induced or not, individual risk assessments based on likelihood-ratios would be helpful. A computer programme using individual information about parity,

cervical status, amount of amniotic fluid, gestational age and maternal age etc. could give individual risks of spontaneous delivery within a few days, caesarean delivery or poor obstetric outcome.

12 Corrections

Paper I:

Table 3- second column: Birth weight **more** than 4500 g

Table 4- * deleted behind P value difference over gestational weeks

13 References

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14 Papers

Dissertations at the Faculty of Medicine, NTNU

1977
1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978
3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979
5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980
6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981
8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983
9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

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14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
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