Chapter 1

General introduction and outline of the thesis

Preterm birth, the problem

Preterm birth is traditionally defined as a delivery before 37 completed weeks of gestation. Approximately 15 million neonates are born premature worldwide yearly, implying a rate of one out of ten neonates[1]. The rate of preterm birth is still rising[2]. Preterm birth is the leading cause of mortality in new-borns[2]. Long-term morbidity in survivors comprises of learning disabilities, hearing loss, behavioural problems and visual disturbances[2]. Inequalities of prevalence and survival rates vary considerably. The prevalence of preterm birth is the highest in Africa and South Asia.

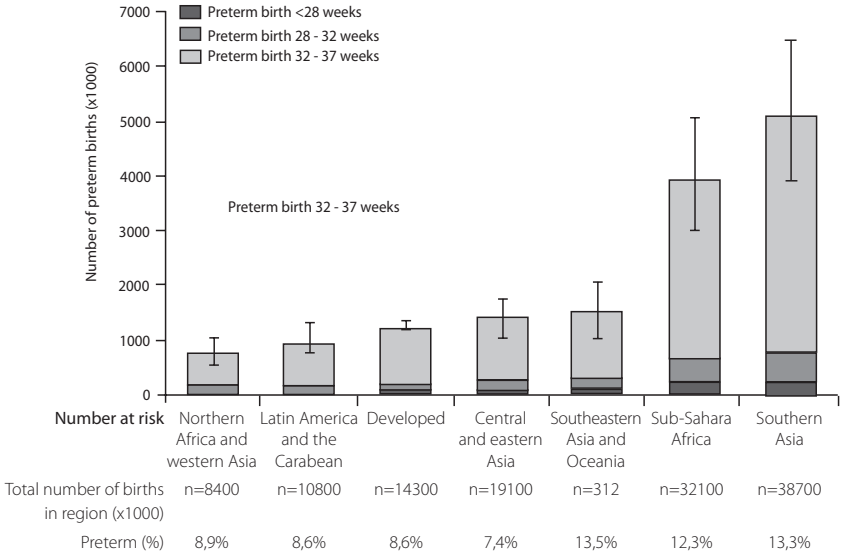


Figure 1. National, regional and worldwide estimates of preterm birth rates in the year 2010 for selected countries: a systematic analysis and implications. Blencowe *et al.* Lancet 379(9832): 2162-2172. By permission.

In developed countries the preterm birth rate is about 8% of all pregnancies[1]. In the Netherlands, perinatal mortality was 9.7 per 1000 total births. Preterm births (> 22.0 weeks and < 37.0 weeks) accounted for 75.3 % of all perinatal mortality with a mortality risk of 82.6 per 1000 births[3,4]. Short-term and long-term effects of preterm birth on society and health systems are profound[5]. Reducing the burden of child mortality due to preterm birth, is therefore one of the eight Millennium Development Goals[6]. Hence, prevention of preterm birth is essential to reduce the high mortality and the considerable risk of lifelong impairment[7].

Perinatal mortality in The Netherlands

Preterm birth is one of the most common causes of perinatal death in the Netherlands. Since the publication of the Euro-Peristat report in 2008, which compared perinatal death rates in different countries in Europe, the Netherlands was forced to attempt to understand the relative high perinatal mortality (1% of all births yearly). Factors that may contribute, are patient characteristics, social and environmental factors and the organisation of the health care system.

The organisation of the Dutch obstetric health care system is different from that in other developed countries. In the Netherlands, care is differentiated in low-risk and high-risk women during pregnancy and delivery[8]. Women with low-risk pregnancies are supported by primary obstetric care providers (midwives and midwifery active general practitioners). In the occurrence of complications or an expected risk on complications during pregnancy or delivery, referral to an obstetrician takes place. Threatened preterm labour and post-date pregnancies are examples for referral[9].

Who is at risk for preterm birth?

Preterm birth can occur spontaneously or for medical reasons (iatrogenic preterm birth). In this thesis we focus on *spontaneous* preterm birth. The two pillars in the strategy to reduce preterm birth are prevention and care for women who present with threatened preterm labour. The underlying pathophysiology of spontaneous preterm birth is not completely understood and has probably multiple causes, which makes prevention strategies challenging.

Care for women with (threatened) preterm birth include interventions such as tocolysis, bed rest or placement of a cervical cerclage. These measures have limited effectiveness[10-12]. The only intervention proven to be beneficial to improve neonatal outcome so far, is the administration of corticosteroids[13]. Consequently, prevention of the onset and identification of the women at risk for preterm birth is essential. The most important symptom of preterm labour is a premature pathological cervical ripening, characterised by a shortening and dilatation of the cervix, which is usually accompanied with increased uterine activity[14].

Various risk factors and methods of screening have been identified. The most important risk factor which predicts preterm birth, is a history of premature birth[15]. Nulliparous women do, however, not benefit from this knowledge. Therefore, most preterm births occur in women initially classified as low risk. A second important risk for preterm birth is a multiple pregnancy. These pregnancies, however, are not the scope of this thesis. In this thesis we focus on singleton pregnancies.

Methods of screening for preterm birth include testing for fetal fibronectin and ultrasonographic cervical length measurement.
Currently, cervical length measurement between 20-24 weeks gestation is thought to be the best method of screening for premature birth[16-18]. A strong association between a short cervix in the second trimester and a subsequent premature birth has been shown by several studies[16-18]. Thus, in a low-risk population of women (defined as nulliparous women and women without a history of preterm birth), women with a short cervical length between 20-24 weeks of gestation are at risk. A screening program is only justified according to the international criteria of Wilson and Jungner (1968), which were updated by the WHO in 2008, if an effective intervention is available[19,20].

Cervical length

Ultrasonographic cervical length measurement is most often used in the clinical setting in women who present with premature contractions. The aim of the measurement is to differentiate which woman will actually give birth prematurely. If the cervical length is above 30 mm in these women, they have a low risk to have a pregnancy complicated by preterm labour[15,21].
The discriminating ability of cervical length measurement is of great value for timely transfer to a university hospital and corticosteroid treatment for fetal lung maturation in case of an imminent premature birth. If these measures are taken in time, improved neonatal outcome can be obtained.
Besides the use of cervical length measurement in women with threatened premature labour, it can also be used for prediction of preterm birth in the absence of contractions. A strong association between a short cervix in the second trimester and a subsequent premature birth is shown by several studies[16-18]. At 20-24 weeks of gestation the average cervical length is within a range of 35-38 mm, measured in singleton pregnancies[16-18]. In 1-2 % of the women a cervical length of less than 15 mm is found, which carries a risk for premature birth of approximately 30%. In 8-10% of women, a cervical length less than 25mm is found, which carries a risk for premature birth of approximately 5%[12,17,18]. The relative risk of preterm delivery was found to increase as the cervical length decreased[18]. Because shortening of the cervical length is associated with preterm birth, the question raises whether a long cervical length is associated with post-term delivery and increased caesarean section rate.

Ultrasonographic examination of the cervix

From an anatomical point of view the cervix is the area where the uterine walls come together to form the narrow end of the uterus, which ends in the vagina. During pregnancy the cervix changes and it will elapse and dilate during birth.

The most reliable method to measure the cervix is transvaginal ultrasound[22-24].

A technically correct cervical length measurement is performed with an empty bladder with the transvaginal probe placed in the anterior fornix. The examiner has to prevent pressure on the cervix by pulling back the probe slightly. This will result in an image with a more or less equally thick anterior and posterior lip of the cervix. The exact mid-sagittal section of the cervix visualises the endocervical mucosa, which should prosecute the whole distance between amnion and external os. After visualisation of the cervix, the examiner has to wait 2 to 3 minutes for any contractions to be detected. Some pressure can be exerted on the fundus to mimic possible shortening by a contraction[25]. The endocervical mucosa is an echogenic line of amnion to the external os. The finding of a discernible echolucent stripe-shaped center, which is the mucus of the cervix, is of no clinical significance.

The calipers must be placed to measure the distance between the internal os and the external os (Figure 2). The cervix is often curved. It is not clinically relevant if the measurement is done in one or several tempos[26]. A curved cervix is always long enough, a short cervix is always straight[27]. If there is a difference between several measurements, the shortest measurement is usually taken as the clinically relevant measurement.

Funnelling is defined as the bulging of the membranes in the internal os. When a cervix is short, funnelling is usually present (Figure 3). Funnelling is not clinically relevant, as it is the shortened cervical length that is the predictive factor for preterm birth[27]. Research shows that the measurement of the cervix is a valid measurement, intraobserver and interobserver variability is small[28-30].

Transvaginal ultrasound is perceived acceptable by women[31]. In women undergoing cervical length measurement 94% experienced little or no discomfort and 98% experienced no or little embarrassment during the measurement[31]. The cervical length measurement itself should be performed using similar technique, to ensure uniformity.

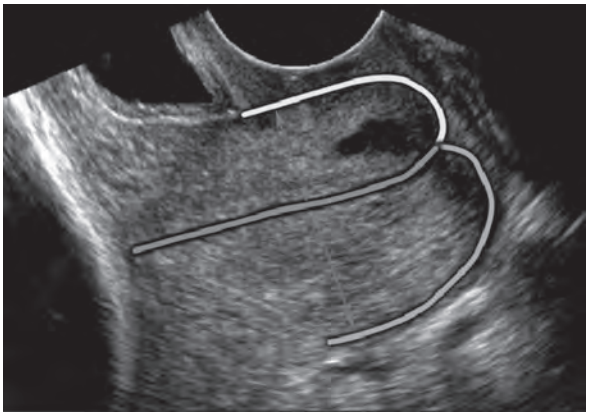


Figure 2 Image of a cervix with the anterior and posterior cervix and the cervical canal in lining.

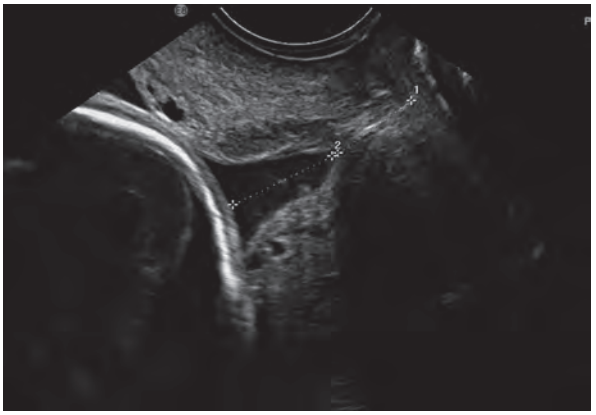


Figure 3 Image of a cervical length measurement with the calipers placed on the internal and external os.

Apart from technical variation in cervical length measurement, several other factors might play a role in the data on cervical length, including parity, anthropometric characteristics, time of the day, unknown uterine activity, infection and bleeding during pregnancy.

Treatment to prevent preterm birth

In the first trimester of pregnancy progesterone plays an important role by endometrial proliferation and sustaining early pregnancy. Progesterone was discovered in the late 20s. It is mainly produced by the corpus luteum in pregnancy. The production is taken over by the placenta after 12 weeks of pregnancy.

Based on these data, it has been postulated that progesterone as a substance might be used to prolong pregnancy in case of an imminent premature delivery. In animal models, a drop in progesterone levels was observed before the delivery occurred[32]. These findings could, however, not be confirmed in humans and the use of progesterone was abandoned for years.

In the 60s a revival of the progesterone theory took place. It was found that a relative drop of progesterone levels had an effect of rising oxytocin and prostaglandin levels[33].

Another important finding was the use of mifepristone (a progesterone antagonist) in termination of pregnancies. Mifepristone induced uterine contractions. This also confirmed the theory that progesterone supports the latter half of pregnancy[33].

Progesterone appears to be important in maintaining uterine quiescence in the latter half of pregnancy[34-36]. It has been shown that progesterone limits the production of stimulatory prostaglandins and inhibits the expression of contraction-associated protein genes within the myometrium, including ion channels, oxytocin and prostaglandin receptors, and gap junctions[37]. Recent studies in a combined high and low-risk population have shown that progesterone reduces the number of premature births in women with a short cervical length at mid gestation[38-39]. Progesterone already seemed to be effective in women with a history of premature birth[40]. A number of studies describe safety of progesterone during pregnancy. These studies comprise about 2000 neonates in total. No difference in the number of congenital anomalies were found directly after birth. In follow up studies (up to 48 months), no differences were found between children who were exposed to progesterone in utero and who weren't[41-44].

Outline and aims of this Thesis

In this thesis studies on spontaneous preterm birth are presented. The main objective was to identify women at risk for preterm birth in a low-risk population and assess the effect of progesterone for the prevention of preterm birth in women who had a short cervical length. The separate aims of this thesis are given below.

Part one: Preterm birth; the problem

- Outline of the risk factors for preterm birth in a review of literature (chapter 2).

Part two: Who is at risk for preterm birth?

- Demonstrate the Protocol of Triple P *screening* and *treat* study (chapter 3).
- Investigate, among women with low-risk pregnancies, the capacity of cervical length measurement to identify women at increased risk for preterm birth. (chapter 4).
- Study the association between adverse perinatal outcome of spontaneous preterm births and the level of care at time of labour onset and delivery. (chapter 5).

Part three: Ultrasonograpic examination of the cervix

- Assess the effect of a cervical length e-learning module on the quality of cervical length measurements in asymptomatic low-risk pregnancies. (chapter 6).
- Statistically analyse the distribution of cervical length measurements, and review the effect of a pre-defined cut-off value (chapter 7).
- Assess the relationship of mid-trimester cervical length and maternal characteristics. (chapter 8).
- Assess the possible relationship between mid-trimester cervical length and its correlation with post-term delivery and intrapartum caesarean delivery. (chapter 9).

Part four: Treatment to prevent preterm birth

- Evaluate the effectiveness of vaginal progesterone in reducing adverse neonatal outcome due to preterm birth, in low-risk pregnant women with a mid-trimester short cervical length. (chapter 10).

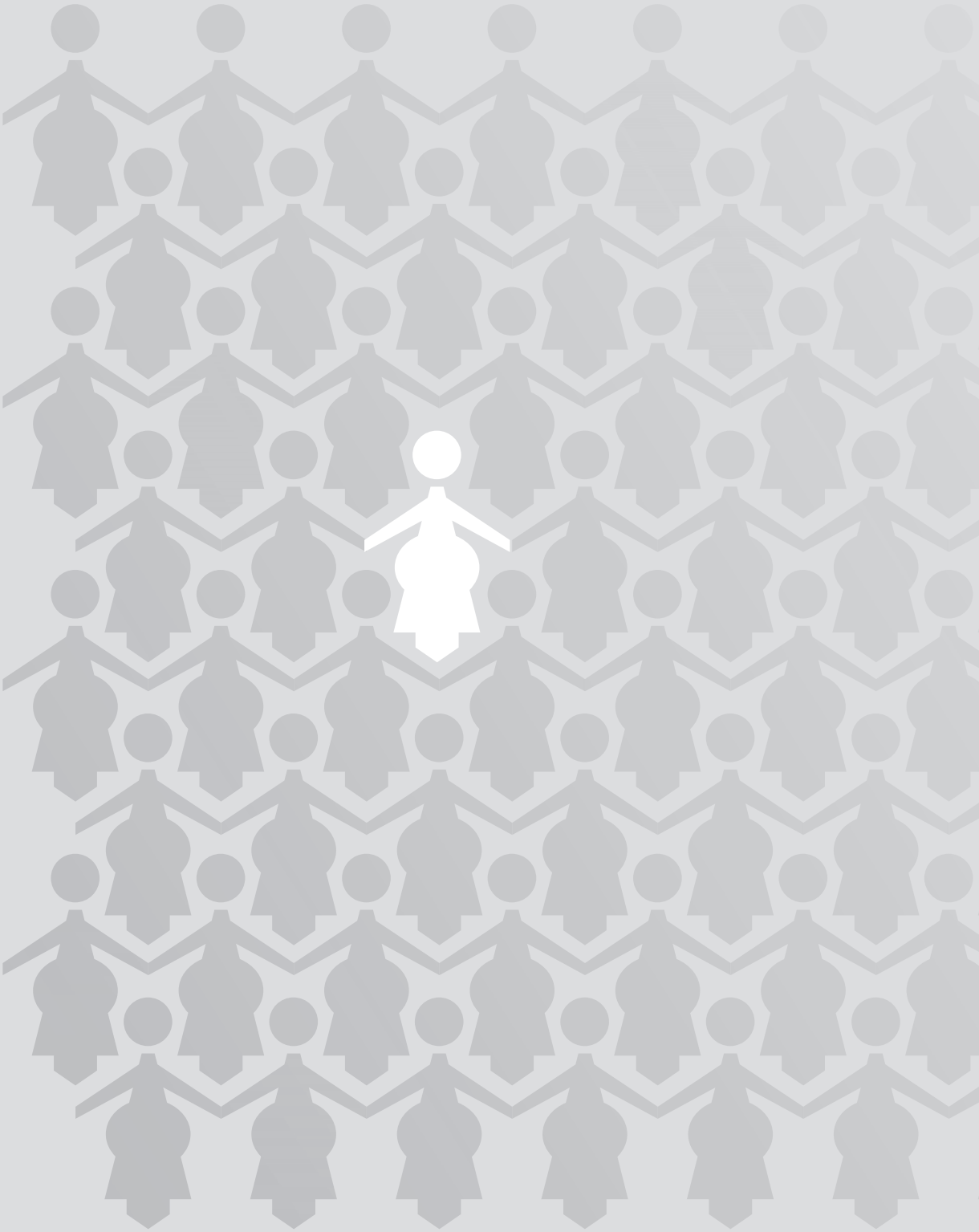
Part five: Women's preference

- Study the preference of pregnant women regarding cervical length measurement and treatment with progesterone in relation to preterm birth (chapter 11).

References

1. Blencowe H, Cousens S, Chou D. et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health 2013, 10(S2)
2. Liu L, Johnson H, Cousens S, et al. Global, regional and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. The Lancet 2012, 379:2151-2161.
3. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC. Trends in preterm birth: singleton and multiple pregnancies in the Netherlands, 2000-2007. BJOG 2011 Sep;118(10):1196-204.
4. Stichting Perinatale Registratie Nederland, Perinatale Zorg in Nederland 2010, Utrecht, Stichting Perinatale Registratie Nederland 2013
5. Blencowe H, Lee AC, Cousens S, et al. Preterm birth associated neurodevelopmental impairment estimates at regional and global level for 2010. Pediatric Research 2013.
6. Millennium Development Goals Indicators http://mdgs.un.org/unsd/mdg/Default.aspx (05-04-2015)
7. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012,380:2197-2223.
8. de Vries R. Midwifery in the Netherlands : Vestige or vanguard ? Med Anthropol. 2001;20(4):277-311
9. Olesen AW, Westergaard JG, Olsen J. Perinatal and maternal complications related to postterm delivery: A national register-based study, 1978-1993. Am J Obstet Gynecol 2003;189(1):222–7.)
10. Smith V, Devane D, Begley CM, Clarke M, Higgins SA. Systematic review and quality assessment of systematic reviews of randomized trials of interventions for preventing and treating preterm birth. Eur J Obstet Gynecol Reprod Biol 2009; 142(1): 3-11.
11. Sprague AE, O'Brien B, Newburn-Cook C, Heaman M, Nimrod C. Bed rest and activity restriction for women at risk for preterm birth: a survey of Canadian prenatal care providers. J Obstet Gynaecol Can 2008; 30(4): 317-26. (ref Lim)
12. To MS, Alfirevic Z, Heath VC et al. Fetal Medicine Foundation Second Trimester Screening Group Cervical cerclage for prevention of preterm delivery in women with short cervix: randomised controlled trial. Lancet 2004; 363: 1849-53.
13. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006(3);CD004454
14. Romero R, Mazor M, Munoz H, et al. The preterm labor syndrome. Ann NY Acad Sci 1994; 734: 414-29
15. Iams JD. Prediction and early detection of preterm labor. Obstet Gynaecol. 101(2), 402-12 (2003)
16. Berghella V, Tolosa JE, Kuhlman K, Weiner S, Bolognese RJ, Wapner RJ.Cervical ultrasonography compared with manual examination as a predictor of preterm delivery. Am J Obstet Gynecol 1997; 177: 723-730
17. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynecol 1998; 12: 312-317
18. Iams JD, Goldenberg RL, Meis PJ et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996; 334: 567-572.
19. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO, 1968.
20. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organisation 2008; 86(4): 317-319.
21. Willms FF, Stralen G, Porath MM, Papatsonis DMN, Oei SG, Mol BWJ. Voorspellen van vroeggeboorte door middel van bepaling van foetaal fibronectine in vaginaal vocht. NTVG 2009; 2009 153: B398.
22 Sonek J, Shellhaas C. Cervical sonography: a review. Ultrasound Obstet Gynecol 1998; 11: 71–8
23. Anderson HF. Transabdominal and transvaginal ultrasonography of the uterine cervix during pregnancy. J Clin Ultrasound 1991; 19: 77–83
24. Brown JE, Thieme GA, Shah DN, Fleischer AC, Boehm FH. Transabdominal and transvaginal endosonography: evaluation of the cervix and lower uterine segment in pregnancy. Am J Obstet Gynecol 1986; 155: 721–6
25. Guzman ER, Mellon C, Vintzileos AM, Ananth CV, Walter C, Gibson K. Longitudinal assessment of endocervical canal length between 15 and 24 weeks' gestation in women at risk for pregnancy loss or preterm birth: transfundal pressure, coughing, and standing in predicting cervical incompetence. Obstet Gynecol 1998; 92: 31–7

26. To MS, Skentou C, Chan C, Zagaliki A, Nicolaides KH. Cervical assessment at the routine 23-week scan: standardizing techniques.Ultrasound Obstet Gynecol 2001;17:217–19
27. Rozenberg P, Gillet A, Ville Y. Transvaginal sonographic examination of the cervix in asymptomatic pregnant women: review of the literature Ultrasound Obstet Gynecol 2002; 19: 302–311
28. Valentin L, Bergelin I. Intra- and interobserver reproducibility of ultrasound measurements cervical length and width in the second and third trimesters pf pregnancy. Ultrasound Obstet Gynecol. 2002;20:256–262.
29. Burger M. Measurement of the pregnant cervix by transvaginal sonography: an interobserver study and new standards to improve the interobserver variability. Ultrasound Obstet Gynecol. 1997 Mar;9(3):188-93.
30. Heath VCF, Southall TR, Souka AP, Novakov A, Nicolaides KH. Cervical length at 23 weeks of gestation; relation to demographic characteristics and previous obstetric history. Ultrasound Obstet Gynaecol 1998;12:304-311
31. Challis JR. Sharp increase in free circulating oestrogens immediately before parturition in sheep. Nature. 1971;229:208.
32. Csapo AI. The 'see-saw' theory of parturition. Ciba Found Symp. 1977;47:159-210.
33. Kovacs L, Sas M, Resch BA, et al. Termination of very early pregnancy by RU 486--an antiprogestational compound. Contraception.1984;29:399-410.
34. Norwitz ER, Robinson JN, Challis JR. The control of labor. N Engl J Med 1999; 341:660.
35. Matthews SG, Gibb W, Lye SJ. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev 2000; 21:514.
36. Norwitz ER, Lye SJ. Biology of parturition. In: Creasy RK, Resnick R, Iams JD, et al, eds. Creasy & Resnick's Maternal-Fetal Medicine, 6th ed. Philadelphia: Elsevier; 2009:69-85.
37. Garfield RE, Kannan MS, Daniel EE. Gap junctions formation in the myometrium: control by estrogens, progesterone and prostaglandins. Am J Physiol 1980;238(3): C81-C89.
38. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007; 357: 462-469
39. Hassan SS, Romero R, Vidyadhari D et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo controlled trial. Ultrasound Obstet Gynecol 2011; 38(1): 18-31
40. Meis PJ, Klebanoff M, Thom E, et al. Prevention of Recurrent Preterm Delivery by 17Alpha-Hydroxyprogesterone Caproate. N Engl J Med 2003; 348(24): 2379-85
41. Resseguie LJ, Hick JF, Bruen JA, Noller KL, O'Fallon WM, Kurland LT. Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota 1936-1974. Fert Steril 1985; 43; 514-9
42. Katz Z, Lancet M, Skornik J, Chemke J, Mogilner BM, Klinberg M. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol 1985; 65: 775-80
43. Yovich JL, Turner SR, Draper R. Medroxyprogesterone acetate in early pregnancy has no apparent fetal effects. Teratology 1988; 38: 135-44.
44. Northen AT, Norman GS, Anderson K, et al. National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) NetworkFollow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol 2007 Oct;110(4):865-72.



Part one:

Preterm birth; the problem