NOW, BUT NOT YET – TENSION IN OBSTETRICS

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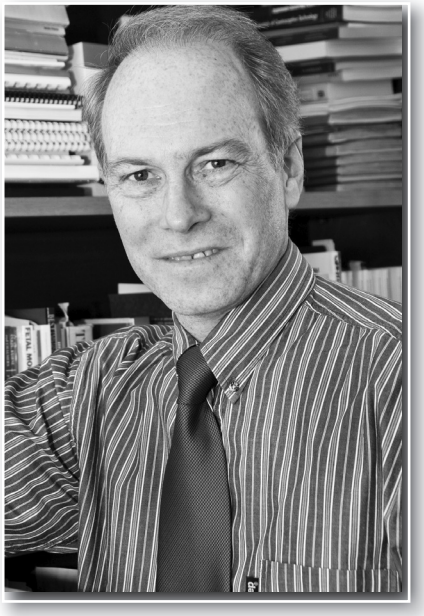

ABOUT THE AUTHOR

David Hall was born in Harare, Zimbabwe, where he began his schooling. He subsequently moved to Durbanville, Cape Town, where he concluded his schooling at Durbanville High School. He completed all his university studies at Stellenbosch University (SU).

After obtaining his MB,ChB degree in 1983, he continued with his studies, specialising in obstetrics and gynaecology (O&G) and staying on as a consultant in the department. He completed his doctorate in 1999 and was appointed associate professor in the same department in 2002.

Although registered as a sub-specialist in maternal-fetal medicine, he has a wide interest across the spectrum of O&G as well as the related fields of education and ethics. He has served as coordinating assessor of all maternal deaths in the Western Cape since 1999. His doctoral research was performed on early severe pre-eclampsia and this topic, together with preterm labour, has been his chief interest of research. Apart from his own local research, he is currently collaborating on a number of international research projects in obstetric medicine.

David is an active teacher at all levels. He places great emphasis on understanding the adult learner and enjoys the dual role of teacher and clinician. He has successfully integrated an electronic resource base into under- and postgraduate lectures. In 2009, he received the Rector's Award for Excellence in Education.

David heads the Obstetric Special Care Unit and acted as national chairperson of the Maternal and Fetal Society of South Africa from January to June 2009. Having registered the sub-specialist course at SU and the Tygerberg Academic Hospital, he is looking forward to training many successful fellows in maternal fetal medicine.

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INTRODUCTION

For most couples, pregnancy is an eagerly anticipated condition. Under normal circumstances, pregnancy begins with conception and, after a period of approximately 9 months (40 weeks), ends with the spontaneous delivery of a healthy baby to a healthy mother.

Pregnancy is also, however, a condition that, under certain circumstances, places the mother at considerable risk. Physiological maternal adaptations to pregnancy, such as increased plasma volume and cardiac output, insulin resistance and hypercoagulability, may also increase the risk of complications in the presence of tissue damage or organ pathology. These changes on the maternal side may be paralleled on the fetal side with the fetus and the placenta able to cause pathological changes in pregnancy. It is therefore not uncommon for an essentially normal pregnancy to develop complications that cause or necessitate delivery remote from term. When an unexpectedly early, urgent delivery becomes imminent, the distant, rosy future is propelled into an immediate, uncertain present and the 'not yet' becomes the 'now'. Two such dangerous complications of pregnancy are pre-eclampsia and preterm labour.

PRE-ECLAMPSIA

Context

Pre-eclampsia is a multi-system, hypertensive disorder affecting 2% to 8% of pregnancies.[1] This condition develops in the latter half of pregnancy and has a multifactorial aetiology that is still only partially understood. When simplified to its clinical essence, pre-eclampsia presents as a constellation of symptoms and signs in the form of a maternal and/or fetal syndrome.[2] The chief characteristics of the maternal syndrome are hypertension and proteinuria. Despite advances in obstetric and neonatal care, pre-eclampsia and its related complications remain a leading cause of maternal and perinatal mortality in both developed and developing countries.[3,4] In addition, the condition has a profound influence on maternal and perinatal morbidity.[5,6] In this context, it is a common referral indication to secondary and tertiary hospitals.

Pre-eclampsia is classified as one of the hypertensive diseases of pregnancy. Once the clinician has diagnosed and classified the condition, it is graded into mild and severe forms. Classification and grading help to direct management and to determine prognosis. In addition, certain investigators believe it important to sub-classify pre-eclampsia further into early and late disease, as early disease, defined as the onset of disease at less than 34 weeks' gestation, is almost always severe.[7] The paradox of pre-eclampsia is that this potentially life-threatening disease usually reverses completely with the delivery of the placenta and, of necessity, the baby.

Upon first consideration, when faced with a pregnancy complication that potentially places the lives of the mother and the baby in danger and that is reversible following birth, prompt delivery seems to constitute a prudent course of action. However, while early delivery is always in the medical interests of the mother, this is not necessarily so for the baby, as delivery at an extremely early gestational age is fraught with complications. Extreme preterm delivery is associated with high perinatal mortality and significant morbidity in the form of lifelong handicap.[8] Furthermore, the situation in all academic hospitals in South Africa is currently complicated by a chronic shortage of the neonatal intensive-care unit beds needed to care for such babies. Taking these facts into consideration, two clinical investigators pioneered a daring alternative.

Expectant management of early severe pre-eclampsia

In 1990, Odendaal et al. from the Stellenbosch/Tygerberg unit published a paper on the expectant versus aggressive management of early severe pre-eclampsia.[9] Four years later, this small study was followed by a slightly larger one from the USA.[10] The goal of these studies was to delay the delivery of mothers with early-onset severe pre-eclampsia to gain time to improve the perinatal outcome. In both trials, carefully selected patients were stabilised and managed by specific doctors in a tertiary institution. Both studies showed improved perinatal outcomes but, due to the small numbers involved, a larger study was necessary

both to confirm the perinatal gain and to document the infrequent adverse maternal outcomes more carefully.

For this reason, a prospective case series over 5 years involving 340 patients with early-onset severe pre-eclampsia was conducted. This study, which is currently the largest prospective case series in patients with this pregnancy complication, showed that an average of 11 days was gained before delivery became necessary for clearly defined maternal and/or fetal indications. An interesting finding was that more time was gained for earlier gestations (Figure 1). This time period enabled fetal-organ maturation to improve, thereby decreasing the need for neonatal intensive-care unit admission and resulting in low perinatal mortality rates at early gestational ages. On the maternal side, 27% of the women experienced a major maternal complication but, because complications were identified early and treated promptly, few women had poor outcomes (Table 1). There were only three admissions (0.08%) to the adult intensive-care unit and the average postpartum stay was not extended beyond that associated with delivery by Caesarean section. The authors concluded that, under carefully controlled circumstances in selected patients, the expectant management of early-onset pre-eclampsia is sufficiently safe for the mother with important perinatal benefits.[11,12]

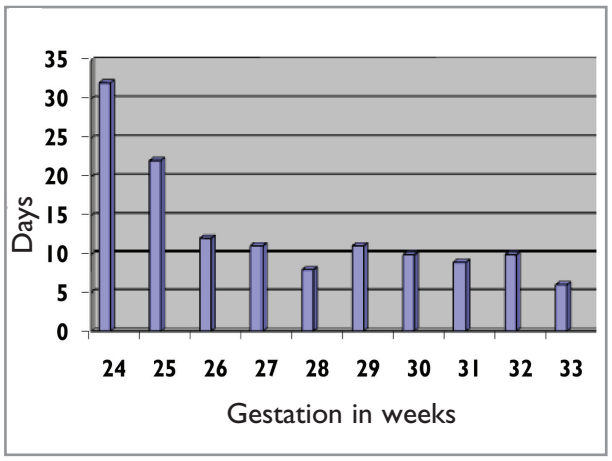

Figure 1: *Expectant management of early severe pre-eclampsia: median number of days gained at each entry gestation*

Table 1: *Expectant management of early severe pre-eclampsia: maternal complications*

Complication	No.	%
Placental abruption	69	20.2
Ascites	37	10.9
HELLP syndrome	18	5.2
Loss of blood-pressure control	18	5.3
Pulmonary oedema	7	2.1
Severe renal impairment	6	1.7
Eclampsia	4	1.2
Intensive-care unit admission	3	0.8
Death	0	
Patients with major comp.	92	27

HELLP = haemolysis, elevated liver enzymes and low-platelets syndrome; some patients experienced > 1 complication.

Following the publication of this large prospective case series, a similar but smaller study was performed in Paris, France, showing this approach to be beneficial, even in well-funded circumstances.[13]

The current situation is that the expectant management of early-onset pre-eclampsia is now much more widely advocated in both developed and developing countries.[14] However, it must be emphasised that this approach is advised only for carefully selected patients managed by experienced clinicians, usually in tertiary institutions.

An important clinical research question that arose from the above-mentioned studies was "How many women with early-onset severe pre-eclampsia actually qualify for expectant management?" The answer was provided by a subsequent prospective case series performed at the Stellenbosch/Tygerberg unit, which showed that almost half (48.5%) of the cases admitted qualified for this approach.[5] The reasons preventing the expectant management of early-onset severe pre-eclampsia are shown in Table 2.

Table 2: *Early severe pre-eclampsia: reasons preventing expectant management*

	n (%)
Viable fetus	69 (79.3)
Early fetal distress	28 (32.2)
Major maternal complication(s) present	24 (27.6)
34 weeks' gestation after stabilisation period	8 (9.2)
Major maternal complication + fetal distress	7 (8)
Intra-uterine death	2 (2.3)
Pre-viable fetus	18 (20.7)
Termination of pregnancy < 24 weeks	5 (5.7)
Intra-uterine death	5 (5.7)
Termination of pregnancy for absent or reversed end-diastolic flow	3 (3.4)
Major maternal complication + absent or reversed end-diastolic flow	2 (2.3)
Major maternal complication + termination < 24 weeks	2 (2.3)
Major maternal complication + pre-viable fetus	1 (1.1)
Total	87 (100)

Pre-eclampsia: other developments

The Stellenbosch/Tygerberg unit is currently collaborating with the University of British Columbia to develop a scoring system using simple clinical and biochemical markers to predict severe maternal morbidity within 48 hours of admission.[15] Some other important contributions from the Stellenbosch/Tygerberg unit to understanding pre-eclampsia have been the investigation of the role of the maternal immune component in the aetiology of pre-eclampsia[16] and, based on the same principles, the influence of HIV on the development of pre-eclampsia.[17] At the level of histopathology, placentas from cases of early and late-onset pre-eclampsia have been carefully examined and compared with controls.[18] This was done to seek further evidence to support the distinction of early from late-onset pre-eclampsia. Finally, in contrast to early-onset pre-eclampsia, late-onset pre-eclampsia has been investigated less and is generally regarded to be mild/moderate disease. However, a careful analysis of cases of late-onset pre-eclampsia at the Tygerberg and Paarl hospitals has revealed that this condition is often complicated by the potentially dangerous condition of eclampsia (13%).[19]

PRETERM LABOUR

Preterm labour is defined as the onset of true labour between a considered point of viability and 36 completed weeks of pregnancy. The condition is further functionally sub-classified as early preterm labour occurring before 34 weeks' gestation and late preterm labour occurring from 34 to 36 weeks' gestation. Second-trimester pregnancy loss and preterm delivery may be considered as elements of an obstetrical syndrome with a multi-factorial aetiology. In this sense, preterm labour presents the same dilemmas as pre-eclampsia and the hypertensive conditions of pregnancy. As mentioned previously, early preterm birth has significant consequences for the newborn baby that specifically revolve around the complications of severe prematurity. However, unlike pre-eclampsia, preterm labour followed by the birth of a severely premature baby often occurs without the mother and/or the baby being medically 'sick'.

Context

Approximately 13 million preterm babies were born worldwide in 2005. Of these, 85% (11 million) were born in Africa and Asia, with Africa having the highest rate of preterm birth (12%). Even in regions where good-quality care is easily accessible, the rate of preterm birth has risen in recent times. In the USA, for example, there has been a 35% increase in the last 25 years.[20] One of the iatrogenic factors leading to this recent increase is the greater accessibility of assisted reproduction, resulting in multiple pregnancies, but this is seldom a significant factor in developing countries, where sub-clinical inflammation and infection play greater roles. There is, of course, a significant health burden associated with preterm birth. The major risks associated with this condition are death, respiratory-distress syndrome, sepsis, intraventricular haemorrhage, necrotising enterocolitis, severe neurological deficits (including blindness and deafness) and developmental disabilities. Studies have reported that preterm birth is the antecedent cause of 36% of infant deaths and 50% of neurodevelopment disabilities.[21–23] Recent publications have shown that, even among late preterm births (34 to 36 weeks), there are still significantly increased rates of neonatal morbidity and mortality.[24] Put together, these findings lead to another inescapable consequence, namely that preterm birth is a leading cause of health-care expenditure.

Interventions

Although preterm birth sometimes occurs as a result of a medical decision (25%), in the majority of cases, onset is 'spontaneous'. Various pharmacological interventions have been proposed and investigated based largely on the basis of our limited understanding of the pathophysiology. Several plausible prophylactic (preventative) medical interventions, such as beta-sympathomimetics, magnesium, calcium and folate, have been shown to be largely ineffective. Progesterone, a natural hormone present in supra-physiological levels during pregnancy, however, has shown promise. It also makes sense to treat conditions such as asymptomatic bacteriuria that may predispose women to preterm labour.[25] Asymptomatic bacteriuria is particularly prevalent among low socio-economic groups, the same groups where preterm labour is most problematic. Once preterm labour has begun, tocolysis (in contrast to prophylaxis) has enabled clinicians to delay delivery in order to accelerate fetal pulmonary maturation and to allow transport to an appropriate institution for delivery. However, it is disappointing to note that tocolysis has still not been unequivocally associated with improved neonatal outcome.[26] Two interventions, one for the prevention of preterm birth and one for the treatment of a specific condition linked to preterm birth, will now be discussed.

Progesterone for prevention of preterm birth

'Progestin' was first isolated from rabbit ovaries by Allen and Corner in 1930.[27] Subsequent to this important finding, the role of progesterone in the maintenance of mammalian pregnancies was well described. It also became apparent that human pregnancies did not persist after the excision of the corpus luteum (producing progesterone) in the first half of the first trimester of pregnancy.

Despite our current understanding, however, there is still considerable speculation as to the exact mechanisms whereby progesterone exerts its favourable influence on the maintenance of pregnancy. As far back as 1974, Csapo et al. proposed the progesterone-withdrawal theory.[28] This theory postulates that, during pregnancy, the high ratio of progesterone to oestrogen allows the uterus to expand but remain quiescent. At the end of pregnancy, the role is reversed as labour approaches and the ratio of progesterone to oestrogen changes, allowing the cervix to ripen and the myometrium to become more contractile, thus facilitating labour. Progesterone is also known to prevent inflammation, a condition clearly linked to labour, specifically preterm labour.[29] Progesterone prevents the formation of gap junctions and inhibits myometrial contractions by down-regulating the expression of contraction proteins.[30]

Clinicians may administer progesterone in one of two forms: natural progesterone (P) may be administered vaginally in the form of a pessary or cream or progesterone may be administered as 17 alpha-hydroxy progesterone (17P), a synthetic caproate ester. When used as prophylaxis, prolonged administration is necessary and a less invasive intervention is therefore preferred. Administered orally, progesterone has variable absorption and is subject to first-pass metabolism and central-nervous system sedation.[31] Administered vaginally, the agent avoids first-pass metabolism and achieves higher endometrial concentrations.[32] This

route of administration is therefore preferable. 17P is administered by injection and has been associated with increased insulin resistance, thus posing a potential problem of gestational diabetes mellitus.

At this point, a few sentinel studies must be presented. In 2003, Meis et al. conducted a double-blind, placebo-controlled, randomised trial among a high-risk population with one or more previous spontaneous preterm births.[33] The active medication was 250 mg 17P, administered intramuscularly every week from 20 weeks' gestation. In this trial, there was a 2:1 (310:153) ratio of active to placebo oil. The primary outcome measure was the occurrence of preterm birth before 37 weeks' gestation. The study showed a significant decrease in the risk of delivery before this gestational age (RR 0.66 [0.54 to 0.81]). The effect was also significant at less than 35 and 32 weeks' gestation. However, it is important to note that 36% of the active-ingredient group still had a preterm birth and that a staggering 55% of the placebo group delivered early. For this reason, prominent clinicians questioned the risk reduction,[34] while others proposed that the placebo injections had actually increased the preterm birth rate.[35] Many questions thus remained unanswered.

The next significant study was also published in 2003, by Da Fonseca et al.[36] Their study population was again a high-risk group, comprising mothers with one or more previous spontaneous preterm births, a prophylactic cerclage or uterine malformation. Vaginal progesterone in the form of a 100 mg suppository was administered daily from 24 to 34 weeks' gestation. This was a double-blind, placebo-controlled trial with a 1:1 ratio of active to placebo agent (72:70), powered to show a decrease in preterm birth from 25% to 12.5%. The results showed that the preterm birth rate in the progesterone group was 13.5% versus 28.5% in the placebo group. This was a significant finding at 37, less than 37 and less than 34 weeks ($P < 0.05$).

Four years later, the largest current trial investigating progesterone for the reduction of recurrent preterm birth was published by O'Brien et al.[37] This trial was a multi-centre, randomised, controlled trial based in North America and included three participating South African centres. The study population consisted of 659 women with one or more previous spontaneous preterm births. They self-administered vaginal progesterone gel (90 mg/day), starting at 18 to 22 weeks and ending with the rupture of their membranes, delivery or at 37 weeks' gestation. The study was powered to show a significant decrease in the rate of preterm birth at less than or equal to 32 weeks' gestation. However, the trial did not show a significant decrease in the frequency of preterm birth less than or equal to 32 weeks or at 35 or 37 weeks. A leading expert in the field described this as an unexpected result.[38] A sub-analysis of the patients in this study did indicate that vaginal progesterone was effective in preventing preterm birth in women with ultrasonographic evidence of a short cervix in the mid-trimester[39] but the trial was not powered for this outcome, although these findings were similar to those of Da Fonseca et al.[40] This begs the question of whether the selection of high-risk women should combine a history of previous preterm birth as well as a short cervix, as measured by vaginal ultrasound.

Trans-abdominal cerclage (TAC) as a definitive intervention

Cervical incompetence is one of the conditions associated with second-trimester loss and extreme preterm delivery. Current evidence suggests that the surgical modification of the cervix in the form of cerclage benefits those with at least three second-trimester losses or preterm deliveries. Patients with two early second-trimester losses and no other identified cause or a previous second-trimester loss and ultrasound findings of a short cervix are also potential candidates.[41] Most often, the cerclage is placed around the cervix using the vaginal route at 12 to 14 weeks.[42] When this less invasive form of cerclage has not been successful or when the cervix is damaged either by spontaneous delivery or by surgical intervention, such as assisted delivery or cone biopsy, however, the vaginal technique may not be possible. Under these testing circumstances, the more invasive TAC may be considered to access the supra-vaginal portion of the cervix. Currently, there are more than 60 pregnancies in the Stellenbosch/Tygerberg TAC series. Up to three pregnancies have been carried after the placement of the initial cerclage and only six losses have occurred in this very high-risk group of patients. When performed by an experienced surgeon on a properly selected patient, this procedure carries the reasonable prospect (90%) of a delivery at or close to term, even among women for whom the goal of a successful pregnancy seemed completely out of reach (Table 3).

Table 3: *Outcome: TAC: 60 pregnancies in 47 women*

Outcome	Before TAC	After
TAC		
T1 miscarriage	36	0
T2 miscarriage	73	6
Delivery 28–33 weeks	13	7
Delivery ≥ 34 weeks	26	47
No living children	22	4
Total pregnancies	148	60
Survival at discharge	25%	90%

CONCLUSIONS

Early-onset severe pre-eclampsia is not uncommon and can be a devastating complication of pregnancy. Under carefully controlled circumstances, however, expectant management is sufficiently safe for the mother and provides important perinatal benefits, with almost half of such cases qualifying for this approach. The recommendations from the Stellenbosch/Tygerberg group have been widely applied. Preventing spontaneous preterm birth and its consequences remains a priority that has been difficult to achieve. There is evidence, however, that women with one or more preterm deliveries and a short cervix may benefit from prophylactic progesterone. Finally, a damaged uterine cervix and/or recurrent mid-trimester losses do not preclude the chance of a successful advanced pregnancy, which can be achieved with the aid of a TAC.

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