Neutral Citation Number: [2019] EWHC 1408 (QB)

Case No: HQ17C00379

IN THE HIGH COURT OF JUSTICE
QUEEN'S BENCH DIVISION

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 10/06/2019

Before :

MR JUSTICE STEWART

- -

Between :

LUC JONES (BY HIS MOTHER AND LITIGATION FRIEND MRS LYNN HARRIS)	**Claimant**
- and -	
TAUNTON AND SOMERSET NHS FOUNDATION TRUST	**Defendant**

- -
- -

Derek Sweeting QC & Adam Korn (instructed by **Sharp, Jackson & Proctor**) for the **Claimant**
Angus Moon QC & Eleanor Morrison (instructed by **Bevan Brittan Solicitors**) for the **Defendant**

Hearing dates: 1st, 2nd, 3rd, 4th, 8th & 22nd May 2019

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

.....

MR JUSTICE STEWART

Mr Justice Stewart:

Introduction

1. The Claimant is aged 23 years, having been born on 5th February 1996. His claim is based on an allegation of brain injury caused by negligence in his mother's antenatal care at Musgrove Park Hospital, Taunton. The alleged negligence concerns the administration to the Claimant's mother, Mrs Harris, of a drug known as Nifedipine during an admission on 25th/26th November 1995 when Mrs Harris was just short of 31 weeks pregnant.

2. Nifedipine is a tocolytic drug, that is to say its purpose is to suppress or postpone pre-term labour. The Claimant's case is that it was negligent to administer Nifedipine. This is denied by the Defendant.

3. The case was listed for trial on breach of duty only. Should the Claimant succeed in respect of breach of duty, there will be a further trial in respect of causation of the Claimant's injuries. In outline the Claimant alleges that the administration of Nifedipine was followed by a fall in maternal blood pressure, leading to a hypoxic episode which caused periventricular leukomalacia (PVL).

4. The Claimant alleges that:

   i) his mother was not in preterm labour;

   ii) Nifedipine should only have been administered as part of a clinical trial and the safety of the drug was not confirmed;

   iii) the drug was administered contrary to the Defendant's own protocol.[1]

Witness

5. The following witnesses were called:

   • Doctor Bett. Her witness statement is dated 22nd November 2017. Doctor Bett is now a general practitioner. In November 1995 she was a senior house officer (SHO) at the Defendant hospital.

   • Mr Eki Emovon. Mr Emovon is a consultant obstetrician and gynaecologist. In November 1995 he was a registrar at the Defendant hospital. His witness statement is dated 17th April 2018.

   • Mr John Hare. Mr Hare qualified as a medical practitioner in 1964. He was a consultant obstetrician and gynaecologist from 1976 until April 1998 when he took early voluntary retirement. He has provided reports dated 22nd June 2018 and 1st March 2019.

[1] Originally this comprised two allegations (i) that Nifedipine should have been administered orally, not sub-lingually; (ii) that there should have been an intravenous line set up prior to the administration of Nifedipine. During the trial the Claimant abandoned allegation (i).

• Professor Steven Thornton. Professor Thornton has been a clinical academic since 1986. He spends about 50% of his working week on clinical work and the remainder on academic work. He is an obstetrician and gynaecologist. At present he is Vice Principal (Health), Queen Mary University of London, and Executive Dean of the Bart's and London School of Medicine and Dentistry. His report is dated 4th February 2019.

6. In addition, there is a joint statement of the two experts dated 12th April 2019.

Authorities

Breach of Duty[2]

7. In *Bolam v Friern Hospital Management Committee*[3] McNair J set out the classic test as follows:

> "…he is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art……Putting it the other way round, a man is not negligent, if he is acting in accordance with such a practice, merely because there is a body of opinion who would take a contrary view."

8. In *Maynard v West Midlands RHA*[4] Lord Scarman said:

> "Differences of opinion and practice exist, and will always exist, in the medical as in other professions. There is seldom any one answer exclusive of all others to problems of professional judgment. A court may prefer one body of opinion to the other: but that is no basis for a conclusion of negligence."

9. *In Bolitho v City and Hackney Health Authority*[5]: Lord Browne-Wilkinson explained and refined the *Bolam* test in this way:

> "……the court is not bound to hold that a defendant doctor escapes liability for negligent treatment or diagnosis just because he leads evidence from a number of medical experts who are genuinely of opinion that the defendant's treatment or diagnosis accorded with sound medical practice……The use of these adjectives - responsible, reasonable and respectable - all show that the court has to be satisfied that the exponents of the body of opinion relied upon can demonstrate that such opinion has a logical basis. In particular in cases involving, as they so often do, the weighing of risks against benefits, the judge before accepting a body of opinion as being responsible, reasonable or respectable, will need to be satisfied that, in forming their views, the experts have directed their minds to the question of comparative risks and benefits and have reached a defensible conclusion on the matter…….

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[2] This section on authorities relating to breach of duty is essentially reproduced from my judgment in *Keh v Homerton University Hospitals NHS Foundation Trust* [2019] EWHC 548 (QB).

[3] [1957] 1WLR 583

[4] [1984] 1WLR 634

[5] [1998] AC 232

…… if, in a rare case, it can be demonstrated that the professional opinion is not capable of withstanding logical analysis, the judge is entitled to hold that the body of opinion is not reasonable or responsible."

10. In *C v North Cumbria University Hospitals NHS Trust*[6] Green J, as he then was, gave a helpful analysis of the case law on breach of duty. He said:

"25. …….It seems to me that in the light of the case law the following principles and considerations apply to the assessment of such expert evidence in a case such as the present:

i) Where a body of appropriate expert opinion considers that an act or omission alleged to be negligent is reasonable a Court will attach substantial weight to that opinion.

ii) This is so even if there is another body of appropriate opinion which condemns the same act or omission as negligent.

iii) The Court in making this assessment must not however delegate the task of deciding the issue to the expert. It is ultimately an issue that the Court, taking account of that expert evidence, must decide for itself.

iv) In making an assessment of whether to accept an expert's opinion the Court should take account of a variety of factors including (but not limited to): whether the evidence is tendered in good faith; whether the expert is "responsible", "competent" and/or "respectable"; and whether the opinion is reasonable and logical.

v) Good faith: A *sine qua non* for treating an expert's opinion as valid and relevant is that it is tendered in good faith. However, the mere fact that one or more expert opinions are tendered in good faith is not *per se* sufficient for a conclusion that a defendant's conduct, endorsed by expert opinion tendered in good faith, necessarily accords with sound medical practice.

vi) Responsible/competent/respectable: In Bolitho Lord Brown Wilkinson cited each of these three adjectives as relevant to the exercise of assessment of an expert opinion. The judge appeared to treat these as relevant to whether the opinion was "logical". It seems to me that whilst they may be relevant to whether an opinion is "logical" they may not be determinative of that issue. A highly responsible and competent expert of the highest degree of respectability may, nonetheless, proffer a conclusion that a Court does not accept, ultimately, as "logical". Nonetheless these are material considerations….The following are illustrations…."Competence" is a matter which flows from qualifications and experience. In the context of allegations of clinical negligence in an NHS setting particular weight may be accorded to an expert with a lengthy experience in the NHS……..This does not mean to say that an expert with a lesser level of NHS experience necessarily lacks the same degree of competence; but I do accept that lengthy experience within the NHS is a matter of significance. By the same token an expert who retired 10 years ago and whose retirement is spent expressing expert opinions may turn out to be far removed from the fray and much more likely to form an opinion divorced from current practical reality…..A "responsible" expert is one

[6] [2014] EWHC 61

who does not adapt an extreme position, who will make the necessary concessions and who adheres to the spirit as well as the words of his professional declaration (see CPR35 and the PD and Protocol).

vii) Logic/reasonableness: By far and away the most important consideration is the logic of the expert opinion tendered. A Judge should not simply accept an expert opinion; it should be tested both against the other evidence tendered during the course of a trial, and, against its internal consistency…….There are 2 other points which arise in this case which I would mention. First, a matter of some importance is whether the expert opinion reflects the evidence that has emerged in the course of the trial. Far too often in cases of all sorts experts prepare their evidence in advance of trial making a variety of evidential assumptions and then fail or omit to address themselves to the question of whether these assumptions, and the inferences and opinions drawn therefrom, remain current at the time they come to tender their evidence in the trial. An expert's report will lack logic if, at the point in which it is tendered, it is out of date and not reflective of the evidence in the case as it has unfolded. Secondly, ……..it is good practice for experts to ensure that when they are reciting critical matters, such as Clinical Notes, they do so with precision……Having said this, the task of the Court is to see beyond stylistic blemishes and to concentrate upon the pith and substance of the expert opinion and to then evaluate its content against the evidence as a whole and thereby to assess its logic. If on analysis of the report as a whole the opinion conveyed is from a person of real experience, exhibiting competence and respectability, and it is consistent with the surrounding evidence, and of course internally logical, this is an opinion which a judge should attach considerable weight to."

Mr Moon QC had some concern about subparagraph (vii) above. It is correct that the critical test of logic is that set out in *Bolitho.* The factors referred to by Green J may well be of assistance in deciding whether an opinion is logical. I do not read him as saying that the mere fact of (e.g.) some internal inconsistency in an expert's evidence means that his opinion must be regarded as illogical.

Mrs Harris' witness statement

11. It was agreed that for the purposes of this hearing the court could read and take into account Mrs Harris' witness statement. There are perhaps only four paragraphs which are of relevance at this stage. I will therefore produce them in full as follows:

> "9. I have two other children; Judy 'Jude' Harris aged 37, and Kimberley 'Kim' Harris aged 27. Neither of my other children suffer from celebral palsy or any other serious illness. When I gave birth to Judy I had an episiotomy to help with the birth. When I gave birth to Kimberley I had an episiotomy and a suction cup was also used.
>
> …
>
> 12. The first two trimesters of my pregnancy were unremarkable. During my third trimester I experienced a number of 'false alarms' where I would believe I was going into labour. On each occasion I would attend Musgrove Park Hospital, Taunton. The false alarms occurred over a period of several weeks.

> 13. Following the last of my false alarms I was treated by a nurse who told me I would **have** to go the full term **(*emphasis added*)**. The nurse provided me with an injection which I was told would stop the onset of false alarms. I did not recall the name of the drug, however I have since been advised that it was called Nifedipine. I cannot remember the exact date of the injection, though I do recall it was several weeks before I eventually gave birth to Luc. It was during the third trimester and I now understand that I was given two doses.
>
> 14. I remember after I was given the injection I was not on the planet, I am able to recall that the bed was tipped up to a near vertical position I understand that this was to restore my blood pressure to an appropriate level.
>
> 15. I did not experience any further false alarms following the injections…"

The medical records

12. I now propose to set out some of the key medical records some of which were attested to by Doctor Bett in her evidence.

2nd November 1995

One record for this date is not in Doctor Bett's handwriting. She is mentioned in the note under her then maiden name, Doctor Garner. The note records that Mrs Harris was admitted from home at 19:15 hours. By dates she was 31+4 weeks pregnant but by USS 27/40. The record shows that premature labour and urinary tract infection were considered as possible diagnoses, Mrs Harris was complaining of abdominal pain/contractions. The pain/contractions were one every three to five minutes, irregular since early morning and more regular since 14:00 hours. A CTG was commenced and the fetal heart baseline was 140 beats per minute (bpm). At 20:05 hours Doctor Garner was asked to review.

Doctor Bett's note records that Mrs Harris was complaining of abdominal pain with a 24-hour history of lower abdominal pains. The pains were now one in five minutes. There was no radiation of the pain. The pain was cramp like. There was no per vaginam loss of liquor. There were no urogenital symptoms and bowel opening was normal. Doctor Bett recorded the history of recent chest infection. Mrs Harris had started that day on Augmentin. She also recorded four previous pregnancies. The first in 1980, a term pregnancy where a girl was born, the second in 1989 when there was a spontaneous miscarriage, the third in 1991 when a girl was born at 38 weeks, and a spontaneous miscarriage in 1992. There is a diagram indicating the area of pain in the lower abdomen. The lower abdomen is described as soft and not tender on palpation. There is cephalic presentation and longitudinal lie. Dr Bett did a speculum examination and determined that Mrs Harris was not in labour. In her statement she says the cervical os was noted to be closed. The notes record: "Speculum: Closed Cx". The midwife noted that the plan was to arrange for an ultrasound scan and await the results of a urine sample sent to the laboratory to exclude urinary infection. Mrs Harris however wanted to go home and said she would phone if she was worried.

9th November 1995

Doctor Bett did not see Mrs Harris on 9th November 1995. However, the midwifery notes (M Dinsdale) record that she was admitted via the GP surgery with possible preterm labour. She had been experiencing pains since the evening before which continued until 5 a.m. and were sometimes as frequent as 1:5. She had had diarrhoea the day before and a feeling of pressure and that something had dropped. Ultrasound had showed breech presentation the week before. The baby was very active and there was no offensive vaginal discharge. The abdomen was palpated. Abdominal CTG was commenced. It appeared reactive. There were good fetal movements. Mrs Harris complained of needing to go to the toilet and then not passing stream of urine. She had just completed a course of antibiotics for chest infection and had been receiving physiotherapy for back problems.

Later at 14:15 there is a note by an SHO which records the presenting complaint as "abdo pains" and refers to the similar admission a week before. It said that she had had a busy day yesterday and reported abdominal pains in the evening which settled. She slept and again had abdominal pains in the morning. There was no per vaginam loss or show. There was no urinary frequency or dysuria. She had loose stools four times the evening before. She admitted to feeling 'a bit uptight' at present. Her pulse was regular, her blood pressure 120/85 and urine showed a trace of protein only. Her abdomen was soft and non-tender. There were no palpable tightenings. Fetal movements were felt. CTG was reactive. The impression was that she was not obviously in labour, so she was reassured and sent home with midwife follow up.

25th November 1995 – first admission

At 17:20 Mrs Harris phoned in feeling unwell with lower abdominal pain.

A note, not written by Doctor Bett and probably written by a midwife (not Mrs Dinsdale), shows:-

At 18:40 Mrs Harris was readmitted from home with a history of backache and abdominal pain since yesterday. It was becoming more uncomfortable today. ? bearing down sensation. Finished course of antibiotics ? a month ago for UTI. ? 'show' yesterday……..On palpation: fundus = 30 weeks. Feels soft. Long lie ? cephalic presentation free. ? LOA fetal heart 140 R. CTG monitoring commenced. Doctor Garner asked to see.

Doctor Bett saw Mrs Harris on the labour ward and recorded that in the last 24 hours she had worsening lower abdo pain which came once in five minutes, now from both sides to pubic area. ? had the show yesterday – pink/mucousy loss. No blood loss. No liquor lost. No UGSx. Bowels opening normally. Good fetal movements. On examination her temperature was 36°C. She was noted as 'well looking'. Pulse 80. BP 110/70. Mrs Harris had a soft abdomen with tenderness over the suprapubic area. Cephalic presentation, longitudinal lie 3/5 palp[7]. Vaginal examination was performed and the cervix noted as 1cm dilated, soft and approximately 1 cm long. The fetal head was not felt and there were no membranes. The note continues: "Speculum multips os'[8]. There was no pooling liquor. Amnistix were negative. The CTG was reactive. The impression was 'early labour' and Doctor Bett prescribed 'betamethasone'.[9] The note continues that the patient was requesting to leave, was strongly advised to stay, but still wished

[7] Doctor Bett said this showed that the fetal head had descended somewhat but was not engaged.

[8] In the multigravid woman the cervix tends to shorter than in the primigravid state and, although the internal os (opening into the uterine cavity) is closed, the external os (opening into the vagina) may allow a fingertip to be inserted into it. This condition is known as 'multips os'. See later

[9] Betamethasone is a steroid.

to go. The registrar was informed and the self-discharge form was to be signed.[10] It is recorded that betamethasone was administered at 20:40.[11]

25th November 1995 – second admission

23:56: Midwifery notes[12] record that Mrs Harris arrived from home again complaining of contractions occurring one every two minutes. She was quite distressed at home. She needed to be reassessed and probably given analgesia. The notes says '? in established labour'. Blood pressure was 130/75, pulse 100. The note continues

"Abdo does tense for short periods quite frequently, doesn't seem to be as often as 2 minutes, but Lynn very uncomfortable."

On palpation the fundus was 32/40. The lie was longitudinal. 'Pres cephalic, position ROL presentation in brim. Fetal movements active.'

At midnight Mrs Harris returned to the labour ward. Doctor Bett wrote that Mrs Harris was complaining of "pains every two minutes now, worsening." There was no per vaginam loss. 'To re-examine cervix please'. The midwife examination was recorded as "soft 1cm dilated. PP 4cm.[13]" The notes then records 'Nifedipine if dilatation of cervix less than 4cm as per protocol. Discussed with registrar and agrees.[14]

The remainder of the relevant notes, save one[15] are not made by Doctor Bett. They show:

At 00:41 abdo CTG commenced – reactive trace. For vaginal assessment for management of care as discussed with Doctor Garner. Doctor Emovon aware of admission. External genitalia normal, vagina moist, cervix sl(ightly) posterior. Thick partially effaced – very gentle examination external os admits a finger – presentation – 4cm above spines. No cord/placenta felt. For Nifedipine regimen as per directions. Baseline BP 133/70. p87.

At 01:00 10mg of Nifedipine were administered. Blood pressure was 112/68. Pulse 88.

At 01:03 Pethidine 100mg was administered. Maxolon 10mg. I.M for analgesia.

At 01:15 blood pressure was 128/69. Pulse 96. Fetal heart rate very reactive – good accelerative periods.

01:20 Lynn in a light sleep. When awake a few minutes earlier complained of abdomen still being painful (in waves).

01:30 blood pressure 137/67. Pulse 36.

01:35 Nifedipine 10mg S.L.

01:45 blood pressure 108/53. Pulse 97.

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[10] The self-discharge form is in the medical notes and is signed by Mrs Harris.
[11] From this it appears that Dr Bett's examination was shortly prior to this.
[12] Seemingly Mrs Dinsdale
[13] The pp of 4cm is the distance between the head to the ischial spines.
[14] Doctor Bett said that the midwife examination note followed the examination at 00:41.
[15] This is the drug prescription sheet which is signed by Dr Bett.

01:49 109/55. Pulse 97.

01:56 101/46. Pulse 120. Doctor Garner alerted. Tx – do not give any more Nifedipine.

The Protocol

13. The 25th November 1995 notes refer to a protocol in connection with Nifedipine. No 1995 protocol has been located. There is this evidence:

• a letter from the legal services manager at the Defendant's Hospital dated 17th September 2010. This letter was written with the assistance of Mr Bidgood, consultant obstetrician and gynaecologist who was working in the Trust at the time of Mrs Harris' pregnancy[16]. Mr Bidgood advised that a protocol must have been followed. Doctor Bett in the notes wrote: 'Nifedipine if dilatation of cervix greater than 4cm 'as per protocol'. The notes therefore imply a protocol was followed for Nifedipine. Mr Bidgood's recollection was that this was a recipe for the dosage and regimen based on the experience of the staff working in Bristol, and using their protocol as the guide. He did not think it was ever printed on separate Musgrove Park based paper, as in those days the Trust was still using guides based on local hospital handbooks.

• Doctor Bett in her witness statement says that due to the passage of time she was unable to recall the exact nature of the protocol to which she was referring.

• Mr Emovon in his witness statement said that he cannot recall a protocol being referred to, but it must have existed otherwise it would not have been agreed.

• There is a witness statement from Alison Garrett, associate solicitor in the employ of the Defendant's solicitors. This is dated 28th March 2018. Ms Garrett sets out the attempts made to locate the 1995 protocol and says that none has been located. Her concluding paragraph says that '… despite the Defendant's best efforts, it has not been possible to confirm the existence of a formal protocol relating to Nifedipine and we have to date, unfortunately not been able to establish any certainty, the source for the entry in the records.'

14. In the experts' joint statement, it is agreed that the 1995 protocol was likely to have been the same or similar to the 1997 protocol which has been disclosed. The Defendant suggests that caution should be exercised before deciding that the precise terms of the 1997 document applied to events in 1995. There is no evidence that it was identical. Indeed, as will appear from the evidence, it seems that it was not identical and may well have differed materially from the 1997.

15. Final submissions were originally listed to be heard commencing at 12 noon on 8th May 2019. At that point Mr Moon QC asked for 15 minutes because of a matter which had very recently come to his attention. This was granted. The court sat again at about 12:20 p.m. It was shown three emails passing between Anne Persey and Robert Fox. Anne Persey was writing in her capacity as legal services manager of the Defendant. Mr Fox was, in 1995, a consultant obstetrician and gynaecologist at Musgrove Park Hospital.

[16] Mr Bidgood's letter of 6 September 2010 was disclosed. This was the basis of the 13 September 2010 letter.

16. After time had been given for consideration, the Claimant indicated that they may wish to apply to strike out the Defence for abuse of process or to adjourn the trial. This application was then made and listed to be heard on 22nd May 2019. Evidence and skeletons were exchanged and further disclosure given. In the event, the application was withdrawn on Monday 20th May 2019 and final submissions took place on 22nd May.

17. The position after hearing the evidence is that it appears that in 1995 there was some document akin to a protocol which recommended Nifedipine. On the balance of probabilities Doctor Bett followed this 'protocol' in prescribing Nifedipine. This she described in her evidence summarised below. It was clearly not the same as the 1997 protocol.

18. There was a suggestion that I might draw an adverse inference due to the failure to call Mr Bidgood or Mr Fox about the 1995 Protocol. However, on analysis this appeared to be more a concern that I might draw an inference favourable to the Defendant based on whatever 1995 document there was. In the circumstances this does not arise.

19. The 1997 protocol was referred to in evidence. Its central contents are:

> "**PRETERM LABOUR**
>
> …
>
> **Introduction**
>
> …
>
> The diagnosis of preterm labour is difficult. Early symptoms may be very subtle and the cervix may dilate with minimal contractions if infection is present.
>
> Preterm labour has several causes. The management differs greatly according to the cause and so it is imperative to consider carefully why a woman has gone into labour.
>
> **PRINCIPALS (sic) OF MANAGEMENT**
>
> Encourage women with any symptoms suggestive of preterm labour to present early.
>
> Admit all women presenting with symptoms to delivery suite for assessment.
>
> Establish or refute diagnosis of labour (this may take hours/days).
>
> …
>
> Consider need for tocolysis.
>
> …

STANDARD CARE

On Admission to Delivery Suite

In addition to any standard management of labour:

1. Review of symptoms	Contractions, mucus show, SRoM & vaginal discharge Abdominal pain & APH. Fetal movements.
2. Institute monitoring	Pulse, BP, temperature. CTG
3. Physical examination	…. Abdominal palpation for tenderness …. Cervix for effacement/dilatation/presentation ….
6. Insert venflon	If APH or suspect occult abruption. If instituting tocolytic therapy. ….

8. Consider need for **corticosteroids** to enhance fetal lung maturity.

TOCOLYSIS

The overall value of tocolysis for the fetus is unclear and it carries some important risks for the mother. It should, therefore, be instituted with care.

The main value of tocolysis is that it gives time for any cortiscosteroid therapy to take effect. It also may allow … utero transfer with greater safety.

Contraindications to Tocolysis

…

>2 cms dilated and contracting strongly

>3 cms dilated

….

Tocolytic Agents

There are various agents available with differing side effects.

Nifedipine (calcium channel blocker)

Salbutamol and ritodrine (B-mimetic agents)

Indomethacin

In general, **nifedipine** is as good as any other agent and is probably the safest drug for mother and baby.

…

Salbutamol and **ritodrine** are poorly tolerated by the women and carry a risk of pulmonary oedema.

Nifedipine Regimen

Site a venflon and start infusion of Hartmann's solution (1 litre over 4 hours)

Check maternal history and auscultate heart for evidence of cardiac disease

Institute electronic fetal monitoring

Give 10mg nifedipine ORALLY

Monitor blood pressure and pulse 5 minutes for 15 mins and then every 10 mins for 45 minutes.

If contractions reduce substantially, repeat nifedipine (10mg orally) every 4 hours for 48 hours.

If little or no effect on contractions, repeat nifedipine at 30 mins and monitor blood pressure again.

If no effect on contractions with 2nd dose, repeat nifedipine at 30 mins (1 hour total).

If no effect again, repeat VE. May be in established labour.

If not in advancing labour at this point, discuss care with consultant.

NB Blood pressure may fall precipitously.

Try to keep the woman lying for fist four hours after initial therapy.

Do not allow her to stand up suddenly or walk unaided.

If BP fails sharply, infuse Hartmann's solution rapidly to resuscitate.

….

GOLDEN RULES
Remember diagnosis of labour is difficult preterm.
….
Use tocolysis cautiously.
…."

Doctor Bett's evidence

20. Doctor Bett was on an obstetric rotation from August 1995 to February 1996. She was therefore half way through this rotation.

Mrs Harris' previous history

21. Doctor Bett said that she first saw Mrs Harris on 2nd November 1995. The medical notes for the patient, including those relating to Mrs Harris' previous pregnancies, would have been available to Doctor Bett at some point. The usual position was that Doctor Bett would look back to an earlier summary page written by a doctor when Mrs Harris was first clerked in during the 1995 pregnancy. If there was no such summary somebody would have to go back through the previous notes.

22. Doctor Bett was taken in cross-examination through entries relating to a previous pregnancy. These entries date from 7th September 1990 to 8th January 1991. In summary they show that Mrs Harris was seen as an outpatient on 7th December 1990, where it is recorded that she had social difficulties and a poorly supportive husband. She was miserable and had abdominal discomfort, though there were good fetal movements. She was seen again on 27th December 1990 with mild contractions approximately every five minutes. Some two hours later the contractions had completely settled with no signs of labour.

23. On 3rd January 1991 Mrs Harris was re-admitted. At 6 a.m. she was recorded as 'still contracting irregularly.' At 7 a.m. the notes say 'painful contractions every 1:3-5. Later she was contracting once every five minutes with moderate to strong contractions. At 18:00 hours she was seen by the consultant and it was decided that she was not in labour and sent home. On 8th January 1991 there is a record of the os uteri being 3cm dilated at 22:00 hours. She was transferred from the labour ward with a possibility that she had been labouring since early a.m. Contractions had almost disappeared by the evening. The next morning she had tightening once every five minutes, the CTG appeared reactive. At 12:45 p.m. Mrs Harris had some tightenings. CTG monitoring suggested contracting mild to moderate. The notes record a slightly blood- stained show at midnight. The following morning she continued to complain of contractions once every four minutes. These were mild on palpation but very uncomfortable for Mrs Harris. At 11:20 on 9th January 1991 the contractions were becoming stronger in a regular pattern, varying in strength. The CTG was reactive. In the afternoon the notes state that Mrs Harris was getting irregular tightenings. It was determined that she was not in labour. Her uterus was soft. She went home.

2nd November 1995

24. Doctor Bett was taken through the medical notes for this date. She accepted that the presentation was similar to the 1990/1991 presentation described above. She said, however, that each time somebody comes in as a patient the history has to be taken and they have to be assessed at that period of time. If a patient complains of contractions, then an examination has to be done so as to assess the situation. On 2nd November 1995 Doctor Bett concluded that Mrs Harris was not in labour despite the history of contractions at quite a high rate.

9th November 1995

25. Again, in relation to 9th November 1995 midwife and doctor's note, Doctor Bett accepted that there was a similar pattern to that in 1990/1991 and on 2nd November 1995. This was a pattern of complaints of abdominal pain and contractions which turned out not to be labour.

25th November 1995 – first admission

26. Doctor Bett prescribed betamethasone which was given at 20:40. It appears that she saw Mrs Harris shortly before that time. She would have been able to see the notes from 9th November 1995 and the midwifery note of the 25th November 1995 admission at 18:40. She would have either looked at the note or discussed the matter with the midwife. She said that Mrs Harris was complaining of pain similar to the 2nd November 1995 and 9th November 1995. She said it is hard to assess, but if a patient says the pain is worsening that has to be considered and a examination has to be done. The diagram of the location of the pain which she made at about 20:40 hours is effectively the same as that she made on 2nd November 1995. It would have been difficult to confirm if Mrs Harris had in fact had a show but that would have to be borne in mind. The possible show the day before would be relevant, because a show is a mucous plug which comes away early on in labour.

27. Apart from the possible show, another difference from 2nd November 1995 and the examination at about 20:40 on 25th November 1995 was that on the first occasion there was no radiation of the pain. On the second occasion pain was radiating from both sides to the pubic area. Doctor Bett thought this was consistent with a contraction.

28. Doctor Bett's examination at about 20:40 on 25th November 1995 included her palpating Mrs Harris' abdomen. It was tender+ - i.e. it was tender but not excruciatingly so. The palpation of the fetal head showed that the head had partially descended but not engaged. She could not feel the head or membranes. 1cm dilation of the cervix represents early dilatation. Her note of multips os recorded a specific appearance. Doctor Bett did not know why she did not note it on 2nd November 1995. The amnistix tests amniotic fluid. The negative result shows that the waters had not broken. At that point Doctor Bett's impression was that Mrs Harris was in early labour. If Mrs Harris had not insisted on leaving, Doctor Bett would have advised her to stay in hospital, having received the steroid, so she could be monitored.

25th November 1995 – second admission

29. The note at 23:56 hours is a midwife note. It appears from the writing that it was a change of midwife from earlier. It was now Mrs Dinsdale. The presentation was, according to Doctor Bett, consistent with the familiar pattern from Mrs Harris. She said

it was difficult to know if the midwife was sceptical about whether there were regular contractions. In re-examination she said that it appears that the midwife did palpate a contraction. This is because the midwife felt tension.

30. Doctor Bett was asked a number of questions about her note at midnight on 25th November 1995. She said that she asked the midwife to examine the cervix. She did not examine it herself. She did not record that she had palpated the abdomen on that occasion. She would work together with the midwife. It appears that Doctor Bett was called and saw Mrs Harris with the midwife who had seen her at 23:56.

31. One of the things to be looked for is progression of dilatation of the cervix. Doctor Bett accepted that she would have been best placed to decide if there had been a change in the cervix, as she had been the person who had examined Mrs Harris earlier that evening. The note at midnight records what she was told and the plan she made. She did not know what she was expecting dilatation to be. From the history she had and the examination of the midwife then, if dilatation was less than 4cm, the protocol suggested prescription of Nifedipine. Doctor Bett accepted that if there had been further dilatation of the cervix that would help confirm preterm labour. She was working to the protocol. She said they were trying to prevent the labour. With contractions and pain every two minutes it seemed as though there was preterm labour.

32. Doctor Bett was taken to the midwife's examination note at 00:41. She accepted that the midwife did not report any dilatation of the cervix. When Doctor Bett wrote subsequently in her note 'M/W: soft 1 cm dilated pp-4cm', she accepted that the dilatation was not in the midwifery note. Doctor Bett said she would have discussed the matter with the midwife and recorded what the midwife told her after her examination. She would have known there was no progression in the dilatation. Mrs Harris was complaining of continuing pain. She was working on the basis of the increase in pain and contractions every two minutes. Looking at the midwifery note, effacement of the cervix would be relevant, as would the fact that the cervix admitted a finger.

33. Doctor Bett did not write down a diagnosis of preterm labour. She accepted that if she was going to make a diagnosis of preterm labour she should have written it down, along with anything relevant to it. She believed that she would have made a diagnosis of preterm labour because the protocol was to prevent such labour progressing.

34. On the drug chart the second entry for betamethasone appears out of chronology. This is because she would have written it up as the second dose to be taken when she prescribed the first dose at 20:40. Then there are three entries for Nifedipine. Doctor Bett would have written those in at the same time. The entries state:

> "26/11/95 – if Cx dilation <4 cms Nifedipine 10mg s/l[17]
>
> 26/11/95 30 minutes later Nifedipine 10mg s/l
>
> 26/11/95 60 minutes later Nifedipine 10mg s/l
>
> - Call if BP less then 100/50 mmHg

[17] Doctor Bett said that 's/l' meant 'sub-lingually'.

- If contractions cease then no further Nifedipine."

It appears the midwife has written against the third prescription: "hypotensive and not contracting so not given."

35. Doctor Bett was asked whether it was right for her to make the decision to prescribe Nifedipine. She said that as a junior SHO she felt that she was part of a good team and well supported with midwives and registrars to guide her. Some registrars may have come themselves to see Mrs Harris. She, Doctor Bett, relayed the information to the registrar on duty and went with what he said at the time.

36. Doctor Bett did not know that Nifedipine was unlicensed. She prescribed it because it was in the protocol. The protocol would be kept in a folder at the nurses' station on the ward. Doctor Bett would have checked it. She would not have asked the patient to consent to the administration of Nifedipine.

37. Doctor Bett would have prescribed the Nifedipine be given sub-lingually presumably because that was in the protocol.

38. Later Doctor Bett was called because Mrs Harris became hypotensive. Therefore, Doctor Bett instructed that the Nifedipine be stopped. She was aware hypotension was an effect of Nifedipine. The notes show the first time Mrs Harris was seen by a registrar was by a Doctor Meates who came on after 8 a.m.

The Protocol

39. Doctor Bett did not remember the protocol. She did not require venflon but, had it been in the protocol, which she was following, she would have ensured this was done. Similarly, if the protocol had said that Nifedipine should be given orally she would have ensured it would be given orally. That is why she says that the protocol must have stated that Nifedipine be given sub-lingually.

40. In general terms the protocol would have said that the drug was there to reduce contractions and prevent labour. If contractions ceased then the protocol would have said that the drug be stopped.

41. Doctor Bett made it clear that she would follow very carefully what the protocol had said. Therefore, where the 1997 protocol states: 'if contractions reduce substantially, repeat Nifedipine (10mg orally) every 4 hours for 48 hours' – that is not consistent with what she wrote. Therefore it would not have been in the protocol she was following. However, the regime for three doses suggested in the 1997 protocol would appear to accord with what she was following at the time.

42. Where the 1997 protocol suggests more than 3cms dilation as a contra-indication, although logically this may equate to less than 4cms, Doctor Bett felt that the protocol she was following would have said less than 4cms.

43. Finally, having prescribed the Nifedipine, Doctor Bett was expecting the midwife to manage the contractions. She interpreted the midwife note at 01:20 that Mrs Harris was complaining of the abdomen still being painful (in waves) as meaning that Mrs Harris was still getting waves of pain i.e. contractions.

Mr Emovon's evidence

44. In paragraphs 13 and 14 of his witness statement Mr Emovon says:

> "13. Doctor Bett has recorded that Nifedipine should be given as per protocol. More than 22 years after the events I cannot now recall what protocol this is referring to, but it must have existed otherwise it would not have been agreed. I can confirm however, it would have been my standard practice to prescribe Nifedipine or other tocolysis to a mother who is 30 weeks in preterm labour with a view to suppressing labour. This would have been in line with my training and general practice at this time.
>
> 14. I understand it is alleged that the second dose of Nifedipine should not have been given at 01:35 on 26th November 1995. I see from the notes that I discussed the case with Doctor Bett at midnight but it is not noted whether we also discussed what the next steps in the mother's care should be. I would have expected Doctor Bett to have called me if the clinical picture significantly changed. Otherwise, I would have expected her to continue to treat the mother as per our protocol and this must have included the second dose of Nifedipine if this was indicated. Had Doctor Bett called me to discuss giving a second dose of Nifedipine I am likely to have agreed that this was indicated because at 01:20 she has noted 'abdomen still being painful (in waves)'. As there was evidence that Ms Harris was still experiencing contractions, I would have recommended continuing with Nifedipine to try and suppress the labour."

45. Mr Emovon said of the note which referred to Mrs Harris' 'abdomen still being painful (in waves)', that 'in waves' conveyed to him severity of pain and suggested that it had become more frequent. He said that if a midwife had said this to him as a registrar he would accept what the midwife said, the midwife being a trained professional. Indeed, he said he would prefer a midwife's examination to that of a freshly qualified SHO.

46. Nevertheless, it would be a matter for the doctor to decide if a second dose was indicated. His opinion, reading the notes, was that contractions were not improving and they were getting worse. Therefore, a second dose was indicated. Somebody i.e. a doctor or midwife would examine the patient to check for contractions. They would examine the abdomen, but also take into account the patient saying that the contractions were getting worse in terms of frequency. He would look at a CTG trace but said that this did not always show contractions. He would not necessarily have expected Doctor Betts to call him to give authorisation for the second dose. If the protocol was there and the situation was getting worse, the SHO would not have to call. He would have expected Doctor Bett to call him if the clinical picture had changed significantly. Although the blood pressure later dropped, within a minute it had picked up from 46 to 54. He did not think that episode of hypotension was significant. If Doctor Bett was comfortable following the protocol, even if the plan changed, then that was a matter for her.

47. Mr Emovon was asked whether he would have expected to have been told about the second dose having been given and that tocolysis was later stopped. His response was that if Mrs Harris had progressed to labour, there was nothing he could do for her. It would then be a matter for the midwives to deliver the baby unless the patient needed a caesarean.

48. In terms of the prescription of tocolysis, Mr Emovon had said in his statement that he did not agree that Mrs Harris was not in preterm labour at the time. She was recorded as experiencing pains every two minutes which were worsening. There was cervical effacement and the cervix was 1cm dilated. In the circumstances, there was evidence that she was in preterm labour although the CTG trace indicated no uterine activity. Having been given the information by Doctor Bett, he must have agreed that she should administer Nifedipine as per the protocol. The information he had at the time was that there was pain every two minutes worsening and the cervix was 1cm dilated. In addition[18] there was the information that the cervix was 'soft'. To Mr Emovon this meant effacing of the cervix, which happens when a woman is going into labour. The pp of 4cm is the distance between the head to the ischial spines. All that information indicated strongly to him that Mrs Harris was in preterm labour. In addition Mrs Harris had come back to the hospital saying the pains were worsening. He was aware of her previous admissions. He said that as a doctor one has to make a judgment as to what is going on at the relevant point. On this occasion she had come back within a few hours of being seen earlier that day in hospital. This he regarded as significant because it was a short time.

49. As to his own position, Mr Emovon said he could have been anywhere in the hospital. He was covering a number of areas. He might have been in theatre. Had he gone he would have examined the cervix and palpated the abdomen for evidence of contractions. He would have looked at the CTG. The fact that it did not show contractions would not particularly matter. He would have palpated the abdomen for regular contractions. He accepted there could be other causes of pain, including urinary tract infection. He said that one of the problems is determining if there is early labour or not. A clinician should err on the side of caution and give tocolytics. It is all a matter of judgment. However, when he was informed on the night, the impression was that Mrs Harris had gone on into preterm labour.

50. As to the prescription of the particular tocolytic, Mr Emovon said that Ritodrine was another possibility. Nifedipine was the drug they used at the time. He went with the first line treatment set out in the protocol unless there were contra-indications. He cannot remember when Nifedipine became the first line treatment. He was a registrar and followed the protocol. During his working history the protocols depended on the hospital and he followed the protocol for the hospital in which he worked. He also relied on the protocol in respect of the administration of the tocolysis.

51. After 26th November 1995 Mrs Harris delivered at term. Mr Emovon said he did not know whether that meant (a) she was in preterm labour on 25th/26th November 1995 and this was inhibited by the Nifedipine or (b) she was not in preterm labour on that night.

[18] This was brought out in re-examination.

52. He said he did not know whether Mrs Harris was multips os or not. If the cervix is dilated then it is dilated. If she had been multips os, then he probably would have given the drug earlier because she would be more likely to deliver.

Mr Hare's evidence: general

53. In Mr Hare's CV he summarises his clinical experience. Prior to being a consultant, he had a special interest in genital infection and also developed an interest in colposcopy, premalignant disease and day care surgery. Between 1976 and 1983 he was a consultant in Cambridge. His CV does not mention particular interests during that period. Between 1983 and 1998 he was a consultant in a district general hospital in Huntingdon. He there maintained his special interest in colposcopy day surgery (especially pregnancy termination and sterilisation) and infection. He did not have any special interest in tocolysis. He has published nothing on tocolysis and has not carried out any research on tocolytic drugs. He managed a labour ward for 15 years and therefore had a lot of experience of tocolysis, but he accepted that Profesor Thornton knows much more about research into tocolysis than he does.

54. In 2000 he was a co-author of a book prepared for lawyers, not doctors. Under the heading 'Management of Preterm Labour' he did not mention calcium blockers such as Nifedipine. He said that in 2000 he was aware there was some movement to use calcium blockers and away from using Ritodrine. He was not aware of the use of calcium blockers, for example in Musgrove Park Hospital or Walsgrave Hospital in Coventry in the 1990s.

55. In paragraph 31 of his Report Mr Hare addressed the question 'should the fact Nifedipine was not licensed for use in pregnancy have influenced this decision?' He describes this as a major consideration and brings into evidence the 2017 data sheet for Nifedipine. He said that when he prepared his Report he was dealing with a 1995 case and the use of the 2017 data sheet was to show that as far as the manufacturers were concerned the position had not changed. He said he was aware of the NICE Guidelines which, with qualifications, recommended in 2015 the use of Nifedipine in preterm labour despite the fact it was not licensed for this use. He did not refer to the NICE Guidelines in his Report. He said he didn't think it was necessary to do so, given that he had referred to the 2002 RCOG Guidance. He thought that was adequate. He said he could have included the NICE Guidance but did not think it necessary. It could have been regarded as relevant, like many other documents. He did not consider he was in breach of the statement of truth of an expert (particularly at paragraphs 3, 7 and 8).

56. Although it will become apparent that I do not accept a number of elements of Mr Hare's evidence, I do not accept that he did not comply with his duties as an expert. He was an honest and respectable witness.

Professor Thornton's evidence – general

57. Professor Thornton's doctorate, awarded in 1989, was for work on Oxytocin. Oxytocin is a hormone active in labour which affects contractions. He was then awarded an MRC Clinician Scientist in 1992 at Cambridge. He said that very few of these are given in obstetrics. It is an award where clinical work is combined with research.

58. In 1998 he was appointed Professor of Obstetrics at Warwick University. His particular interests were in early labour which included dealing with tocolysis. He led the speciality on behalf of the RCOG. His work consisted not only of how the uterus contracts, but also on labour and how to help women in childbirth. This covered many aspects of childbirth including tocolysis. He oversaw a lot of documents which came out of the RCOG. His role in respect of a number of documents was an oversight role.

59. As Professor of Obstetrics one of the things Professor Thornton had done was to found and become Chair of the Clinical Study Group for preterm birth. He brought together a number of obstetricians from the UK who were interested in preterm labour and birth. He was responsible for setting up the group. It led to recognition by the National Institute of Health Research. This is an organisation run under the Department of Health which undertakes, and is responsible for, all areas of research in medicine.

60. Listed as a clinical interest of Professor Thornton is 'preterm labour'. This involves a large proportion of his research time and complements his clinical interest in the management of preterm labour. He frequently lectures on this at national and international meetings. He has written numerous guidelines and chapters for clinical texts. He set up a specialist preterm labour clinic at UHCW which received regional and national referrals. He now undertakes clinical obstetrics at Barts NHS Trust where he assists the development of a specialist preterm labour clinic.

61. Professor Thornton lists co-authorship of over 130 publications. In addition, he has been responsible for a number of plenary presentations. In particular:

    i) For the SGI in Atlanta in 1999 he was symposium organiser for 'calcium and myometrial contractility.' The SGI is the Society for Gynaecological Investigations. It is the major clinically based research organisation in the United States. This was acknowledged worldwide as a major conference. The subject matter was in relation to contractions and the effect of calcium.

    ii) In 2014 there was a presentation in Jordan heading 'Preterm Delivery Prevention'. This was dedicated to tocolysis.

62. Professor Thornton said he was invited around the world to talk about current and recommended treatment of preterm labour. He said that he hoped that his views are taken seriously in relation to preterm labour and tocolysis. There is always discussion in the area. He has spent much of his working life dealing with preterm labour.

63. In clinical practice Professor Thornton developed and led a specialist antenatal clinic for women at high risk of preterm labour. This attracted regional and national referrals. There were three protagonists, Professor Shennon from London, Professor Jane Norman from Edinburgh and Professor Thornton in the Midlands[19]. The three Professors set up preterm labour clinics and worked together to provide high quality care to women with preterm labour problems.

64. Criticisms were made of Professor Thornton as an expert witness. While I accept his evidence for the most part, there are certain matters whish require careful consideration

[19] Professor Jane Norman was the Chair of the NICE Guideline Committee which reported in 2015.

in this regard. However, as with Mr Hare, I reject any suggestion that he did not comply with his duties as an expert. He, too, was an honest and respectable witness.

Was Mrs Harris in threatened preterm labour?

Preliminary

65. In the joint statement the experts agree that preterm labour is labour before 37 weeks gestation. Threatened preterm labour would be preterm contractions with or without cervical dilation. The same would be true for the term 'suspected preterm labour'. As for 'early preterm labour' this could mean labour in early pregnancy or early in the process of labour. The experts assumed the latter; a reasonable definition therefore would be labour before the signs and/or symptoms are fully established or early in the process of established labour. All these terms were in common or regular use in 1995. The term 'preterm labour' covers all the other above terms. In the literature and in the evidence, terms were used interchangeably, though Professor Thornton sought to keep to the term threatened preterm labour. I have generally tried to do the same; however, unless stated to the contrary the expressions should be regarded as co-terminous.

66. The experts also agree that in 1995 the use of tocolysis was reasonable/justified for threatened or suspected preterm labour. However, administering tocolysis involves administering a drug with side effects. It is common ground that it should not be given as a prophylactic.

67. Mr Hare did not disagree with the statements in two books which are very similar. One extract states[20]:

> "The term threatened preterm labour is often used to describe pregnancies complicated by episodes of clinically significant uterine activity but without cervical change."

Mr Hare's opinion was that if the court decides that the notes in the present case record significant uterine contractions (i.e. not Braxton Hicks contractions) then the criteria for threatened preterm labour were satisfied.

68. In the joint report Professor Thornton says that the administration of tocolysis was definitely justified because Mrs Harris had preterm contractions and no contraindications. Mr Hare says that the diagnostic threshold had not been reached.

69. It is agreed that the diagnostic threshold for (threatened) premature labour at which tocolysis should be instituted can be difficult. Mr Hare's opinion on paper in summary is:

i) the criteria for diagnosis of preterm labour[21] required (a) gestation 20-37 weeks and (b) documented uterine contractions (four in twenty minutes or eight in sixty minutes) and (c) if membranes are intact then documented cervical change by a

[20] Turnbull's Obstetrics 1995 (Walkinshaw)
[21] Besinger and Niebyl cited as authority in the Defendant's 1997 protocol; agreed by Walkinshaw in the chapter 'Preterm labour and delivery of the preterm infant' pages 609-627 from Turnbull's Obstetrics 2nd edition 1995.

single examiner or cervical effacement of greater than 75% or cervical dilatation of greater than 2cm.

ii) Mrs Harris was in the period of 20-37 weeks gestation;

iii) As to uterine contractions, the note at 23:56 reading 'c/o contractions occurring 1:2' has to be read in the context of the midwife's examination where she wrote 'abdomen does tense for short periods quite frequently. Doesn't seem to be as often as every few minutes but Lynn very uncomfortable.' Mr Hare says that he has never known a midwife to make a positive diagnosis of labour without recording the strength and frequency of the contractions, and that the phraseology indicates to him that the midwife was far from convinced that labour had started. His opinion is that the only acceptable way to clarify this position would have been to set up a CTG tracing and look for evidence of contractions. The short section of CTG trace obtained before Nifedipine was given showed no evidence of regular uterine contractions.

iv) As to the changing condition of the cervix, the 25th November 1995 note at about 19:00[22] performed by Doctor Bett read '1cm dilated cervix about 1cm long. Head not felt'. On visualisation with the speculum multips os was recorded.[23] The midwife's examination at 00:41 on 26th November 1995 shows the cervix as slightly posterior, thick, partially effaced, external os admits a finger, presentation 4cm above the spine.' According to Mr Hare, this is not any different, apart from in the form of words, from the first examination. Therefore, Mr Hare says that there was no cervical change.

v) The diagnosis of preterm labour requires skill and experience. The senior resident obstetrician should have assessed the case, rather than the diagnosis being made by the SHO on the basis of history and without the confirmation of the examination findings obtained by the midwife.

Mr Hare's evidence

70. Mr Hare was extensively cross-examined. I shall attempt to condense his evidence in cross examination in this way:

Doctor Bett's examination findings

71. Mr Hare accepted that the note recording that Mrs Harris had perhaps had a show was relevant in that a show can be a sign that labour is about to begin.

72. Doctor Bett's examination note at about 20:40 hours of 25th November 1995 recording that the cervix was 1cm dilated, was soft and about 1cm long was the subject of discussion:

a) as to the length of the cervix Mr Hare said that in a multigravid woman, the cervix can start from a length of 2-3cms. He agreed that a cervix of

[22] In fact probably nearer to 20:40

[23] See later. It was not put to Doctor Betts that her finding that the cervix was 1 cm dilated was an inaccurate finding or that it was in effect a finding of multips os.

less than 1.5 centimetres at 30 weeks, if a matter of measurement, is a risk factor for early delivery.

b) dilatation is another sign that a woman might be going into labour;

c) if the cervix is soft that is a characteristic of early labour;

d) Mr Hare did not accept any of these findings as being accurate from a junior SHO. In respect of the cervical os he said that that was probably multips os rather than true dilation. He said the assessment of the cervix being soft, hard or in between is a difficult one. It was pointed out to Mr Hare that he had not previously suggested that the measurement of the length of the cervix or the assessment of its softness was inaccurate; therefore this had not been put in cross examination to Doctor Bett;

e) in the joint statement Professor Thornton had said that a cervix at 30 weeks described as soft and admitting a finger is characteristic of a change associated with early labour and not a multip os. Mr Hare agreed that <u>if</u> the two observations were in fact correct then he would agree with Professor Thornton's conclusion.

f) Professor Thornton had further said 'it is not usual for the cervix to admit a finger at 30 weeks suggesting that it was not a multip os.' As to this, Mr Hare said that depended on whether the finger was through the external or internal os.

Contractions:

73. In relation to contractions:

a) Mr Hare said that contractions were an essential description for early labour. In relation to Doctor Bett's entry,[24] Mr Hare said that there was rhythmic pain every five minutes and contractions were a possibility but there were other explanations. At 23:56 the complaint was of more frequent contractions occurring once every two minutes;

b) the midwife's examination at 23:56 suggested that she did lay her hands on Mrs Harris' abdomen and felt the tension and the frequency. He also accepted that these were probably uterine contractions, but not necessarily those of labour. He said that the notes suggested a degree of indecision. He interpreted the note as the midwife not believing that she was feeling meaningful contractions. He said that a midwife would not write in this way if recording such contractions. She would record the word 'contractions' and would write how long, how strong and how frequent the contractions were. As to note at 01:20, he regarded this as history, not an examination by palpation.

c) Mr Hare acknowledged, when he was taken to it, the fact that the next morning the same midwife had written 'contractions (irregular)' in the

[24] About 20:40 on 25th November 1995.

antenatal inpatient care plan. He said he would have expected her to use the word contractions at the time of the original entry;

d) after exploration of the matter, Mr Hare accepted that the most likely explanation is that Mrs Harris had uterine contractions, though he thought they were probably Braxton Hicks rather than true early labour contractions.[25] Mr Hare said that Braxton Hicks contractions are normal uterine contractions of which the mother is aware. It is variable whether they demonstrate a change in frequency. Generally, they would not be associated with cervical change. Professor Thornton explained that the uterus in pregnant, and in non-pregnant, women undergoes contractions. Towards the end of a pregnancy the mother feels these contractions. They are usually irregular, and are a normal finding not indicative of labour. They are usually felt later in pregnancy than the stage at which Mrs Harris was, i.e. 30+ weeks. His reading of the notes was that Mrs Harris was not having Braxton Hicks contractions.

e) Mr Hare was asked whether if rhythmic contractions were palpated there was sufficient evidence to justify tocolysis. He refuted this, saying that it was important to take into account the frequency, duration and strength and that these were not recorded or estimated. Further, CTG lower tracing showed no evidence of uterine activity;

f) Mr Hare's opinion was that to diagnose preterm labour it is essential to have a record of the frequency duration and estimated strength of contractions. Also, that these would usually show on a CTG trace which was not the case here. As regards the recording of frequency, duration and estimated strength of contractions, he accepted that he could not point to any literature to support this.

Mrs Harris' History

74. Dealing with Mrs Harris' history of preterm contractions in earlier pregnancies, Mr Hare said that this was more or less neutral. He did not accept that there was a distinction because the earlier pregnancy complaints were at 35-36 weeks and not 31 weeks. It was put to him that Professor Thornton had said in the joint report that women with recurring contractions are at an increased risk of preterm delivery and that is known that social issues are associated with an increased risk of preterm delivery. Mr Hare accepted this, but said that on the other hand the earlier pregnancies needed to be put into the equation; also that social issues can be associated with complaint of contractions which are not established. However, Mr Hare accepted if the correct diagnosis was made on 25th November 1995 as to early preterm labour, then the earlier pregnancies were not relevant.

In final submissions the Claimant relied on the earlier admissions to say that Mrs Harris had previously been attended by Mrs Disdale who had noted 'contractions', yet no

[25] Mr Hare accepted that in his Report he had missed (paragraph 13.3 and 29.1) inserting Doctor Bett's finding at about 20:40 on 25th November 1995 of a worsening lower abdominal pain over the previous 24 hours with the pain coming every one in five minutes and from both sides to the pubic area. In the joint report he had not opted for Braxton Hicks contractions as being the probability. He had suggested the possibility of bladder or bowel as the pain source – a possibility he did not maintain in cross-examination.

tocolytic was given and the contractions settled after observation. The most relevant notes in this regard are on 8th January and 9th January 1991. However: (i) A finding of contractions does not necessarily lead to a diagnosis of threatened preterm labour – though it may do; (ii) a doctor has to make a judgment, based on contractions and other indicators. Medicine is an art, not a science; (iii) Doctor Bett had made a number of relevant findings on the 1st admission on 25th November 1995 which had given her an impression that Mrs Harris was in early labour, such that she was very concerned when Mrs Harris discharged herself; (iv) the fact that Mrs Harris had settled without tocolysis is unremarkable, since as repeated below, it is not possible in advance to identify which women, even if they can properly be diagnosed as having threatened preterm labour, will then progress to established labour.

CTG Tracing

75. In relation to CTG tracing:

Mr Hare accepted that in neither of the two textbooks which he had cited[26] was it suggested that there needs to be CTG confirmation of contractions before making a diagnosis. Nor was this in the 2015 NICE Guidelines. He also accepted that there were some circumstances in which a CTG would not pick up changes in the contours of the abdomen. The CTG does not measure contractions themselves but the secondary effects of the contractions. Nevertheless, he was of the opinion that it was essential to use CTG tracing to diagnose preterm uterine contractions in clinical practice. It is common ground in the present case that the CGT does not show any contractions.

76. Mr Hare had referred in the joint statement to seven pieces of literature. It was put to him that in those papers the CTG was not used to diagnose threatened preterm labour, but rather to determine whether the women were eligible for the trial. He said that that begged the question. Mr Moon QC took him to two papers namely:

a) Thornton et al (2015)[27]. Mr Moon QC suggested that the requirement for CTG was to decide who should be in the study. Mr Hare said that it was the criterion for the methodology which allowed the diagnosis to be made; that was essentially the same as to whether to diagnose in the clinical situation. Mr Hare did not accept that this 'proof of concept' study, requiring CTG as an entry criterion, was totally different from the position in clinical practice.

b) The second paper was Kragt and Keirse[28]. Mr Moon QC suggested that there is nothing in this article which supports what Mr Hare said about the need for a confirmatory CTG. Mr Hare referred to two passages. The first says that abdominal pains were defined as 'vague' if they were not of a rhythmic character, if there were no clinically recognisable contractions on palpation and cardiotocography, and if there was no watery or bloody discharge. Mr Hare said that this was an assessment of clinical practice with a view to giving advice. Abdominal pains would

[26] Turnbull's Obstetrics 1995 (Walkinshaw); James and others 'High Risk Pregnancy Management Options' 1994 Chapter 11.
[27] 'Treatment of spontaneous preterm labour with retosiban: a phase 2 proof-of-concept study'. 2015: Brtitish Journal of Pharmacology 740
[28] British Journal of Obstetrics and Gynaecology 1990 Volume 97 pp. 317-323.

not be vague if they were rhythmic and clinically recognisable as contractions on palpation and/or CTG. The second said:

> "clinical assessment on arrival was always complemented with cardiotocography. Urine analysis, laboratory investigations and ultrasound were performed when deemed appropriate."

Mr Hare did not accept that this was because it would be important to know the fetal heart rate, not to know about contractions. He said that, on the contrary, heart rate monitoring and the sensation of contractions go together. The CTG is an invaluable tool in the assessment of both. The fact that the last sentence was about the well-being of the fetus did not change his opinion on this. It seems to me that the paper does not support Mr Hare's statement in the joint statement that it stresses that CTG should always be used.

(c) Mr Hare said he would wish to qualify other passages in the Kragt and Keirse paper. This was where they said their study indicated that women were reasonably accurate in their diagnosis of threatened preterm delivery, and that there is little room for improving the woman's own diagnosis of threatened preterm delivery. The paper concludes with the following:

> "This implies that a considerable amount of research will be necessary before the obstetrician's diagnosis of preterm labour will become substantially better than the woman's own diagnosis."

Mr Hare pointed out that this study was a prospective observational study i.e. with no controls. It was testing the proposition in another paper (O'Driscoll 1977) that suggested that about 80% of diagnoses of signals of impending preterm birth by the mother herself, were erroneous. He said that from his experience an 80% error rate was a little harsh; he would put it at somewhat under 50%.

Tocolysis prescription – general considerations

77. It is of importance to note that a diagnosis may have to be made under some time pressure because the experts agree that there may be a point after which the process of labour is irreversible. Therefore, failure to act may render treatment ineffective. Professor Thornton in his report said 'it is considered that once labour is fully established, it is unlikely that the process can be significantly delayed. For this reason, threatened preterm labour is usually diagnosed on relatively soft criteria.' In the textbook[29] the authors say:

> "…because of the need for early management of suspected preterm labour, the diagnosis is commonly made in clinical

[29] How accurate is a woman's diagnosis of threatened preterm delivery? High Risk Pregnancy Management of Contractions.

> practice before the above criteria are met, and hence the reported incidence of threatened and actual preterm labour may be open to question."

Professor Thornton added in evidence that the risks of not treating with tocolysis are high. A baby born at 30 weeks has a 4-5% chance of dying. If a baby is born at less than 32 weeks, the risk of brain injury is high. Therefore, when thinking whether to give tocolysis, the decision is heavily weighted in favour of treatment, and that is standard practice. Such is the perceived advantage that some US studies will not do placebo controlled trials on the basis that it is unethical not to treat with tocolysis in threatened preterm labour. Professor Thornton agreed that tocolysis should not be used prophylactically. He said one should look at the symptoms and signs and investigations (if applicable) in each individual case to see if tocolytic treatment was or was not appropriate. However, it is not possible to identify in advance which women will progress from threatened preterm labour into established labour.

78. Although the above window of opportunity is important and requires action rather than prevarication, that does not detract from the fact that there is a diagnostic threshold which should be reached before prescribing tocolysis. The diagnosis may be difficult, and doctors acting non-negligently may mistakenly diagnose threatened preterm labour and properly prescribe tocolysis. Nevertheless, as Professor Thornton himself wrote in the 1995 Yearbook of the RCOG: "…any possible improvement in fetal outcome must be offset by the risks of exposing the mother and fetus to the hazards of treatment. This is particularly important in preterm labour since uterine activity often spontaneously abates. The judicious use of tocolysis is thus of paramount importance and these drugs must be administered in clinical practice with the same rigour that is required in research."[30] Part of the problem is that there was, and is, difficulty in proving that tocolysis actually improves outcome, such that it is also reasonable not to use them[31]. Careful consideration should therefore be given before prescribing tocolysis.

79. There is thus a difficult assessment to be made between using care before prescribing and not missing the opportunity to prescribe. In the present case, however, if Mrs Harris was, or was reasonably thought to be, having true, early labour uterine contractions at a rate of about 1 in every two minutes or thereabouts, then the administration of tocolysis was not in breach of duty.

Post 2nd dose - evidence

80. Professor Thornton was asked about certain matters following the 2nd dose of Nifedipine[32].

81. In relation to whether Mrs Harris had been experiencing true contractions at 11.56 and thereafter until the Nifedipin was stopped:

(i) At 0212 on 26th November there is a note "not contracting". The use of the word 'contracting' may imply either that the midwife would normally use that word explicitly

[30] See also the 1997 Protocol and an extract from Vatish et al (2005): Management of threatened preterm labour" of which Professor Thornton was a co-author.
[31] E.g, see RCOG Guidelines 2002.
[32] Mr Hare was not asked about these notes. They were substantially reproduced in his Report, though he appears not to have drawn specific conclusions from them..

if there were contractions; alternatively, that this was in contradistinction to earlier and therefore connotes that what was felt earlier were contractions. Professor Thornton said this note was not explicit as to whether it was as a result of an examination or Mrs Harris' complaint. In any event, this was after two doses of Nifedipine[33].

(ii) Later, at 0305-0320, Mrs Harris complained of extreme back pain. As part of the examination, no contractions were palpable

(iii) At 0920 is a note: "Remains uncomfortable – tightenings intermittent".

(iv) Professor Thornton's interpretation of these notes was that Mrs Harris had been having contractions which had then stopped at about 0212 after two doses of Nifedipine[34]

(v) On 3rd December 1995 Mrs Harris was admitted with a presenting complaint of "Tightenings every 2 minutes….staying same intensity". On examination the contractions were noted as not registering a great deal on the CTG. Vaginal examination was "multips os, not effaced, posterior." The impression was "Braxton Hicks contractions. ? threatening preterm labour". The plan was to admit, give Betamethasone 12 mg 12 hourly. It was recorded that when she was given Nifedipine on the last admission she had low blood pressure.

Professor Thornton said that one would not give tocolysis a second time. Steroids were given because the doctor was perhaps still worried about preterm labour. As to the cervical findings, he said he was not sure what, if anything, they added, though they did make him wonder if Mrs Harris just has a sensitive uterus. He said that one could not look back from these notes for assistance on whether Mrs Harris was or was not in threatened preterm labour on 25th/26th November 1995. I accept this evience.

Mrs Dinsdale - Midwife

82. One of the matters to be addressed is that Mrs Dinsdale, the midwife who made the notes at 23.56 and onwards on 25th /26th November 1995 has not provided a witness statement and has not given evidence. Therefore her notes have had to be interpreted by others. The Claimant submits that I should draw inferences adverse to the Defendant in accordance with *Wisniewski v Central Manchester HA*[35]

83. In *Wisniewski,* the Court of Appeal said this:

"(1) In certain circumstances a court may be entitled to draw adverse inferences from the absence or silence of a witness who might be expected to have material evidence to give on an issue in an action.

(2) If a court is willing to draw such inferences they may go to strengthen the evidence adduced on that issue by the other party or to weaken the evidence, if any, adduced by the party who might reasonably have been expected to call the witness.

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[33] This note also needs to be read in the context of the notes by Mrs Dinsdale on the drug chart and also later that morning on the Antenatal In-Patient Care Plan – see below.
[34] He also referred to the midwife's Antenatal In-Patient care Plan Note at a time before 0615 – see above
[35] [1998] PIQR 324

(3) There must, however, have been some evidence, however weak, adduced by the former on the matter in question before the court is entitled to draw the desired inference: in other words, there must be a case to answer on that issue.

(4) If the reason for the witness's absence or silence satisfies the court then no such adverse inference may be drawn. If, on the other hand, there is some credible explanation given, even if it is not wholly satisfactory, the potentially detrimental effect of his/her absence or silence may be reduced or nullified."

84. *Wisnieski* was recently considered by the Court of Appeal in *Manzi v King's College Hospital NHS Foundation Trust*[36]. At [30]-[31] the Court said:

> "30. There are three aspects to the claimant's submissions that demonstrate the difficulty that she has on this issue. First, *Wisniewski* is not authority for the proposition that there is an obligation to draw an adverse inference where the four principles are engaged. As the first principle adequately makes plain, there is a discretion i.e. "the court is *entitled* [emphasis added] to draw adverse inferences". An appellate court will be hesitant to interfere with the exercise of such a discretion given that it is being exercised in the knowledge of all the nuances of evidence that are in the knowledge of the judge who receives that evidence. Second, the judge in this case did not conclude that an absent witness had to be central to the case, he merely and correctly identified that the doctor in *Wisniewski* was central to that claim as the person who had failed to defend his clinical judgment. By comparison, the judge decided that Dr Hooper's role and hence evidence was tangential for the reasons I have summarised…. Third, there was an explanation for absence and that was a decision on proportionality grounds taken by the defendant i.e. this was not a case where a defendant or witness deliberately prevents or avoids the admission of evidence that would undermine their case.
>
> 31. There is also a further difficulty that the claimant must face. On 21 August 2015 Master Roberts gave case management directions. The claimant sought a direction for disclosure of information about Dr Hooper but did not seek an order that she file and serve a witness statement. They could have asked for the latter. If the claimant was of the view that Dr Hooper's evidence was as important to her case as is now asserted and that an adverse inference would be appropriate in Dr Hooper's absence, they could have asked for a direction which contained the warning that an adverse inference may be drawn if the evidence was not provided. Even without such a direction, the claimant could have made arrangements to obtain evidence from Dr Hooper themselves."

[36] [2018] EWCA Civ 1882

85. What is the factual position in this case regarding Mrs Dinsdale? Witness statements were served by the Defendant on 19th April 2018. A year later, and shortly before trial, the Claimant's solicitors wrote on 17th April 2019 referring to the clinical notes and asking for the full name of the midwife, whether she was in receipt of an NHS pension and about the efforts that the Defendant had made to contact her. The Defendant responded on 25 April 2019 saying that the midwife was called Mrs Dinsdale and she had left the Trust in 1997. They had contact details for her, she was no longer practising as a midwife, and she had not responded to the solicitors' request that she review the records and provide a witness statement. They were aware she does work for the NHS but had no knowledge of her pension arrangements

86. In considering whether I should draw an adverse inference, the following factors are relevant:

- No allegation of negligence has been made against Mrs Dinsdale. This differs from the situation in *Wisniewski*, where the doctor who did not attend was alleged to have been negligent. He had also provided a witness statement.

- This was not a case where there had been a tactical decision not to call Mrs Dinsdale so as to deliberately prevent or avoid the admission of evidence that would undermine the Defendant's case

- A credible explanation had been given as to why Mrs Dinsdale had not been called; even if it was regarded as unsatisfactory, then no adverse inference should be drawn[37]. It appears that the Claimant did not appreciate her potential significance until just prior to trial. The potential relevance of her evidence was perhaps appreciated to some extent by both sides, but it appears that it did not occupy 'centre stage' for them until recently. I do not find the Defendant's explanation to be unsatisfactory.

- As in *Manzi* [31], no direction had been sought that Mrs Dinsdale should file and serve a witness statement, failing which an adverse inference might be drawn; also the Claimant could themselves have made arrangements to obtain evidence from her.

- Evidence from Mrs Dinsdale would have been preferable to others trying to interpret her notes.

- Nevertheless in my discretion I believe it would be wrong in the circumstances to draw an adverse inference.[38]

Discussion

87. In this discussion section, I will take into account the preceding evidence, refer to further evidence from Professor Thornton, and come to conclusions as to whether it

[37] See also the recent Supreme Court case of *Prest v Prest [2013] UKSC 34 at [44]*.
[38] The Claimant in written submissions relied on the duty of candour under Regulation 20 of the Health and Social Care Act (Regulated Activities) Regulations 2014. The Defendant said it was not applicable. The Claimant accepted it added nothing to the common law position in these circumstances. I therefore do not deal with it further.

was reasonable for the Defendant to consider at the time of the administration of Nifedipine that she was in threatened preterm labour.

88. 2nd November 1995: The complaint was of abdo pains/contractions which had been irregular, but had become more regular. No contractions were detected. There was no tension/tenderness on palpation. The cervix was closed. Professor Thornton said he would be a little concerned about the possibility of threatened preterm labour, but this note gave him a different feeling from the notes on 25th November[39].

89. 9th November 1995: Mrs Harris was admitted via the GP, with ?preterm labour. Professor Thornton said that if a GP was in doubt about abdominal pain, then s/he would want to exclude preterm labour. The presenting complaint was abdominal pain. His interpretation of the pain being "sometimes as frequent as 1:5" was that it did not tell us anything about frequency and it suggested that it was not always 1:5. It is not known if Mrs Harris volunteered this information or if she was asked (e.g.) whether the pain was constant and, if not, how often it came and went. The report to the SHO was abdo pains during the evening which had settled; Mrs Harris had slept and then the pains came again in the morning. There were no palpable tightenings. Although there was a record of diarrhoea the previous day, which made Professor Thornton less concerned about possible labour, he agreed that there was no definitive diagnosis of the cause of pain.

90. Professor Thornton said that these two admissions would have increased his sensitivity to the possibility of preterm labour. A woman who has a history of complaining of contractions may give rise to an increased possibility of preterm labour.

91. 25th November 1995, 1st admission: at 18.40 the presenting complaint to the midwife was of backache and abdominal pain since the preceding day, and of a possible show. On palpation the midwife did not find any tension/contractions. Later (probably shortly prior to 20.40):

(i) Doctor Bett recorded a history of worsening lower abdo pain coming every 5 minutes now and from both sides to the pubic area. Professor Thornton said that Doctor Bett had said that she felt this was consistent with contractions; he agreed that this was a reasonable assumption.

(ii) As to the possible show, this has to be distinguished from just bleeding. Doctor Bett had entered a description of the show as a "pink/mucousy loss". Professor Thornton said that a true show can herald the onset of preterm labour. The fact that Mrs Harris in fact went to term does not suggest that she probably did not have a show, since it is possible to have an early show and still go to term.

(iii) Doctor Bett palpated the abdomen. She recorded "tender+". Professor Thornton agreed that she had not recorded contractions or tension. There was no note of uterine activity being discovered.

[39] Professor Thornton was criticised for this expression and other similar expressions about his impressions of the notes. It was said that this is hopelessly vague, falls far short of satisfying a reasonable criterion for diagnosis, speculative and is not evidence-based. While it is not, and was not presented as powerful evidence, it is nonetheless evidence of some weight and demonstrates that Professor Thornton was careful not to exaggerate in this regard.

(iv) On vaginal examination the cervix was recorded as 'soft', 1 cm dilated and about 1 cm long. Professor Thornton said that these, if correct, are signs that labour may be coming[40].

At that stage the Doctor Bett did not make a diagnosis of preterm labour, though Professor Thornton's opinion was that a case could be made for prescribing tocolysis. It appears that she did not because there was still a possibility that Mrs Harris was complaining of abdominal pain which might settle. Professor Thornton said that his concerns were a little heightened because of the cervical findings, the complaint of pain radiating to the pubic area and the history of a possible show.

92. It is of note that Doctor Bett's note was that her impression was that Mrs Harris was in early labour. She strongly advised Mrs Harris that she should not discharge herself as Doctor Bett wanted to keep her under observation, presumably because she was worried that she might be threatening preterm labour. A steroid, Betamethasane, was prescribed. It is steroids which are given to improve lung development in the premature foetus. However, they take a day or two to work. Tocolysis stops the contractions, so giving the steroids time to work. Usually the two drugs are prescribed at the same time. Prescribing a steroid at about 20.40 would presumably be as a precaution given the impression of early labour. Professor Thornton said that the threshold for giving a steroid is lower than for prescribing tocolysis.

93. 25th November 1995 2nd admission: the midwife's note at 23.56: On this admission Mrs Harris complained of contractions occurring 1:2. The midwife (Mrs Dinsdale) palpated the abdomen and found that it tensed for short periods, quite frequently, though it did not seem as often as once every 2 minutes. Mrs Harris was very uncomfortable. The tension was felt suprapubically. What if any difference was there from the position earlier that evening and on the two previous admissions earlier in November? Professor Thornton said:

(i) A complaint of contractions every two minutes (allowing for the fact that the midwife did not think the tensions were as often as that[41]) did not sound like a bowel or bladder problem. It indicates that something is happening and, on that history and finding on examination, in conjunction with the earlier history and findings) he would make a diagnosis of preterm labour.

(ii) The midwife did not use the term contractions, but in his mind there was little doubt that she was describing contractions. He asked rhetorically what else was causing Mrs Harris to tense? He could not think of another reason for tensing other that voluntary tensing. The tensing was suprapubic. If Mrs Harris was tensing intentionally or because of pain, it would not just be felt suprapubically.

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[40] He was shown a table prepared by Mr Hare of recorded findings throughout Mrs Harris' pregnancy between 2nd November 1995 until 30 January 1996. These findings showed some variability after 25th November 1995 in these signs, and in effacement. Professor Thornton said it was not known whether, in a single pregnancy, signs could in effect reverse.

[41] It is not known how many tensings for short periods the midwife felt. However, some supportive evidence that they were happening frequently, even if not every two minutes, is that her note is timed at 23.56 and Dr Bett's note is timed only 4 minutes later, at midnight – however there may be some discrepancy in precise timings e.g. Mrs Dinsdale may have written her note at 23.56 rather than begun the examination at that time.

(iii) The midwife did not record the strength[42] of the contractions. It is not possible to determine the strength of contractions from palpation. Palpation can only detect movement of the lower abdomen. Midwives can make an estimate based on palpation and complaint of the woman so as to assess whether the contractions are important enough to make labour progressive.

(iv) Although the note might be regarded as "marginally inadequate" in terms of what is actually written down, and could have been better expressed, in practice the midwife would discuss with the doctor and a diagnosis would be made together.

(v) The description of the findings on palpation and the complaint made by Mrs Harris is not consistent with Braxton Hicks contractions. Women do not come in complaining of contractions every two minutes if they are Braxton Hicks.

94. I shall pause at this stage of the narrative to make certain findings. They are these:

(i) In general I accept the above evidence of Professor Thornton. I find that as at 23.56 Mrs Harris was complaining of, and found by the midwife on palpation to have, contractions which were not Braxton Hicks. I also find that it was, or would have been, reasonable to diagnose threatened preterm labour.

(ii) On no abdominal examination in this pregnancy prior to 25th November 1995 had tenderness been found.

(iii) On no occasion in this pregnancy prior to 25th November 1995 had the presenting complaint clearly been one of contractions on a regular basis. Here the complaint was of contractions every two minutes and the finding was of quite frequent tensing, albeit not seeming to be as often as every two minutes; also Mrs Harris was described as 'very uncomfortable'. Professor Thornton said that by regular contractions he meant contractions occurring consistently; if he had to put a frequency on it, which perhaps he should not, he would say once every 5 minutes or more often.

(iv) Shortly afterwards the SHO prescribed Nifedipine. Her note is succinct. However, I accept what Professor Thornton said, namely that it would be standard practice for the doctor to communicate with the midwife. Doctor Bett did not record a complaint or finding of contractions in her note at midnight, but if there had been contractions that would have been communicated to Doctor Bett. Therefore I agree with Professor Thornton that the absence of a recording of contractions or tensing in Doctor Bett's note is not that important – though it would undoubtedly have been better to have recorded contractions. That she understood that Mrs Harris was contracting is apparent from her note on the drug chart, to which I shall turn in a moment. The note on the drug chart evidences that Doctor Bett appreciated that tocolysis was to be used only in the presence of contractions. Also, if a doctor wanted to prescribe and a midwife disagreed, Professor Thornton said he would expect that to be recorded.

(v) The Drug chart written up by Doctor Bett after midnight but prior to the administration of Nifedipine stated: "..if contractions cease then no further Nifedipine". We know that, later, Mrs Dinsdale followed the instructions in terms of the doses of

[42] Professor Thornton was shown the Partogram of Mrs Harris' subsequent labour. This contains a box with key diagrams of mild, moderate or strong contractions for filling in the form. Professor Thornton said midwifes do assess the strength, but cannot really do so by palpation.

Nifedipine which should be administered and when she did not give a 3rd dose. Is it at all likely that Mrs Dinsdale would have administered two doses of Nifedipine if she did not believe that what she had found at 23.56 were contractions? I find that to be very unlikely. In addition, when she wrote up why she was not administering the 3rd dose she wrote: "Hypotensive and not contracting so not give." This, too, indicates that Mrs Dinsdale considered that Mrs Harris had been contracting at the time of the 1st and 2nd dose. She was following the mandate of Doctor Bett. Therefore the probabilities strongly favour the fact that the midwife found, and told Doctor Bett, that Mrs Harris was having contractions and that they were more regular than earlier, even if not quite as regular as the complaint of 1:2.

(vi) The evidence of Mr Emovon, now a consultant obstetrician, was essentially in agreement with Professor Thornton's opinion. Doctor Bett herself said it appeared from the midwife's note that she felt tension, that she did palpate a contraction.

(vii) Mrs Dinsdale recorded on the Antenatal in-patient care plan at sometime before 0615 on 26th November 1995: "Contractions, (irregular) settled whilst on labour ward with nifedipine/pethidine treatment given breakfast". This is a difficult note. Doing the best I can, it appears that the note is recording a historical position, i.e the position earlier that morning. This follows from the fact that the contractions are recorded to have settled with nifedipine/pethidine. Thus the fact that Mrs Dinsdale uses the word 'contractions' here suggests that what she described earlier were, in her opinion, contractions. This is entirely consistent with my above finding. The difficulty is that those contractions were described as 'irregular'. The Claimant says that it is supportive of them being Braxton Hicks. What did Mrs Dinsdale mean by 'irregular'? The problem is that there is nothing in the 23.56 (or 0120) notes to suggest irregularity; the suggestion is, if anything, rather to the contrary. This is especially so when one has regard to Professor Thornton's evidence that by regular contractions he meant contractions occurring consistently. Also, a midwife would be expected to know about Braxton Hicks and their distinction from true uterine contractions. There may be other explanations of what Mrs Dinsdale meant: unfortunately she did not give evidence, so we are in the dark. However, this one word is not sufficient to undermine the other evidence on which I have relied to find that Mrs Harris was having true uterine contractions when Nifedipine was administered. Further, Professor Thornton said that although the note says 'irregular', his reading is that the contractions were uterine, even though Braxton Hicks tend to be irregular. Looking at the note, Mrs Dinsdale did not find the contractions to be as regular as the complaint of 1:2; this may be why she later used the word "irregular'. However in her note she then added: "but Lynn very uncomfortable". This may explain why she considered them to be true contractions, not Braxton Hicks

(viii) Contractions are the key element in making a diagnosis of threatened preterm labour. If they were not present, generally speaking tocolysis should not therefore be administered. However, other signs, taken together with contractions, would be part of the picture of the diagnosis. So:

- The cervix was recorded by Doctor Bett to be closed on 2nd November 1995. On 25 November 1995, Doctor Bett's vaginal examination found it to be 1cm dilated, soft and 1cm long. There may be some difficulty in precise measurements done digitally, and the Claimant suggests that there was no dilatation, rather multips os. Professor Thornton said that multips os is essentially a closed cervix, with a slight

dimple. He would not have expected the cervix of a woman 30 weeks pregnant to admit a finger. The finding of a soft cervix was itself of some significance. Professor Thornton said the length of the cervix was important because a short cervix is associated with marked increase in preterm delivery. He said that 1.5cm is used as the cut-off measurement for a short cervix. Although a 1cm digital measurement cannot be regarded as precise, this finding would go into the equation.

- The possible show on 24th November 1995, the history of Mrs Harris being admitted on the previous occasions complaining of pain, possibly contractions, and the increasing frequency of the pains, would all indicate an increased possibility of preterm labour.

- Thus the findings earlier were consistent with threatened labour and then contractions were complained of and found on examination by the midwife.

95. Doctor Bett was consulted at midnight. Apart from recording the fresh history and the fact of discussion with the Registrar, her note merely sets out the regime for prescribing Nifedipine, subject to the midwife confirming that the cervix was less than 4cm dilated. Though Doctor Bett does not note a diagnosis of preterm labour or threatened preterm labour, she said in evidence that she was trying to prevent labour and it seemed with the contractions/pain every 2 minutes that there was preterm labour. It also appears that she had diagnosed it at this point, as she decided (so long as the cervix was found to be < 4cm dilated) to prescribe Nifedipine. This was Professor Thornton's understanding.

96. At midnight there was no further cervical examination by Doctor Bett. No progress in dilatation is recorded by the midwife or Doctor Bett. This appears to be because, in Doctor Bett's opinion, the die was cast for the Nifedipine administration, assuming < 4 cm dilatation.[43]

97. At 0041 the abdominal CTG was commenced. The midwife made some findings on vaginal examination. Nifedipine 10 mg was then administered at 0100 following Doctor Bett's prescription.

(i) As to the CTG, this did not demonstrate contractions. I accept Professor Thornton's evidence that CTG is not diagnostic of preterm labour and that there is no literature which says it is. There is no good way of measuring uterine contractions. The 'toco' line of the CTG (the bottom line) is not used in the diagnosis of preterm labour as there are often false positives and false negatives[44]. In the studies the position is very different from in clinical practice. The purpose of the studies is to develop drugs and it is necessary to understand if contractions reduce. Therefore, in order to be admitted to the study, the subjects have to be restricted to those where the CTG in fact did show contractions, so as to see if they changed in frequency. Professor Thornton was not persuaded that the tocodynanometer (the bottom line sensor) had been properly applied as it was very flat at times.

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[43] In cross examination, Professor Thornton said that if dilatation had reached 1cm an hour he would have been extremely concerned because labour would then have been fully established and may not have been capable of being stopped. He said that it did not matter hugely what the state of the cervix was unless it was dilated such that it was too late to administer tocolysis.

[44] This was not the language he used but it was the gist of his evidence.

(ii) As to the examination, (a) the cervix admitted a finger. It was described as (b) slightly posterior and (c) partially effaced. According to Professor Thornton, (a) would not be expected in a woman 30 weeks pregnant, (b) suggested that it might be starting to move, as happens at the start of labour, (c) suggested that the cervix was starting to be taken up.

98. I therefore find that Mrs Harris was probably having true, early labour uterine, not Braxton Hicks, contractions, and that there were other indicators such as the possible show (amplified as 'pink mucousy loss'), and a soft, 1 cm long, 1 cm dilated cervix[45]. Therefore it was reasonable to prescribe tocolysis. Although Doctor Bett did not record a diagnosis of threatened preterm labour, she did in fact make this diagnosis. It was reasonable to make this diagnosis.

Was it negligent to prescribe Nifedipine?

99. As mentioned, both experts agree that if preterm labour/threatened preterm labour was a proper diagnosis, then tocolysis was indicated to allow steroids to operate so as substantially to reduce the risk to the fetus. Mr Hare says that that if a tocolytic drug was indicated, that drug in 1995 should have been Ritodrine. The Defendant accepts that it would not have been a breach of duty to use Ritodrine. Mr Hare says that it was a breach of duty to prescribe Nifedipine.

100. The two drugs are of different types. Ritodrine is a member of a group variously described in the literature as Beta-sympathomimetics/beta-agonists of Betamimetics. Nifedipine is a calcium channel blocker.[46]

101. Mr Hare accepted that it is probable that the Defendant's 1995 protocol[47] recommended Nifedipine. He accepted that if it did recommend Nifedipine then it probably discouraged the drug which he would have prescribed, namely Ritodrine. In those circumstances it would not be Doctor Bett, the SHO, who would be criticised for prescribing Nifedipine. The central complaint is that the protocol/recipe was negligent in its recommendation. He said that when Protocols began to be introduced in the 1990s, in a District General Hospital it was usually a consultant who would write the Protocol on a particular topic. The consultant would do the research before writing the Protocol. The Protocol had to contain a balanced view of the evidence at the time, especially if it was recommending the use of a new drug. Mr Hare said he did not regard the 1997

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[45] I have reviewed some of the evidence as to the finding by Doctor Bett on the 1st 25th November admission that the cervix was 1cm dilated and her recording after Mrs Dinsdale's 0041 examination that the cervix was 1cm dilated. This may have been a finding of multips os, as Mr Hare's table of earlier and later findings does not suggest cervical dilatation on other examinations. As I have previously stated it was not put to Doctor Bett that her finding of 1cm dilatation was multips os. On balance I am persuaded that the cervix was 1cm dilated. The note of the 1st 2th November 1995 admission makes it clear that Doctor Bett made two findings (i) on VE 1cm dilated; (ii) speculum: multips os – thereby suggesting that, though junior, she appreciated the difference. In any event, some dilatation would not be necessary for a diagnosis of threatened preterm labour.

[46] Other drugs have been considered for inhibiting preterm labour. These are Indomethacin (a cyclo-oxygenase inhibitor/prostaglandin inhibitor), Glyceryl nitrate (a nitric oxide donor), magnesium sulphate, Atosiban (an oxytocin receptor antagonist) and Acebutolol (a Beta adrenergic receptor blocking agent). Some of these have come more prominently into play since 1995.

[47] It was probably less thorough than a protocol because Mr Bidgood in the solicitor's letter had apparently referred to it as a 'recipe'. For full details of Mr Bidgood's letter, see below.

Protocol (or the 1995 Protocol assuming it similarly recommended using Nifedipine as the tocolytic drug of choice) as a balanced view, taking account of the available literature at the time[48].

102. In summary it was Mr Hare's opinion that in November 1995 no reasonable body of clinicians in the UK should have been using Nifedipine as tocolysis.

103. Professor Thornton's opinion was different. He said that in 1995 Ritodrine was the treatment of choice, but, because of its side effects, there was a move to introduce other drugs. By that date it was acceptable to use Ritodrine or Nifedipine (and some others).

104. Professor Thornton was cross-examined on certain extracts in his report. In summary these were:

"**Brief History of Tocolysis**

…….

12. As nifedipine increased in popularity in the 1990's, ritodrine was essentially phased out. The Royal College Guidelines from 2002 state that if a tocolytic drug is used ritodrine no longer seemed the best choice…

Oxytocin Antagonist

13……Thus, in the 1990's the only licenced treatment was ritodrine which was considered to be associated with more adverse effects than nifedipine……..

General comments on case

16……..She was given nifedipine which was standard practice at the time. Although ritodrine was licenced for use as a tocolytic, it was associated with marked maternal side effects and was falling into disrepute……I consider that nifedipine should have been used in preference to ritodrine at this time given the data available. Indeed I consider that a significant proportion of obstetricians would have used nifedipine in this situation. Given the major competitor for nifedipine (atosiban) was not licenced until 2000, nifedipine was the first choice tocolytic at the time. I therefore consider that the management of Mrs Harris with nifedipine was appropriate and consistent with standard practice……

Comments on amended particulars of claim (undated)

….

(ii) it was contrary to the 1997 Protocol to use tocolysis continually

……

The administration of nifedipine was favoured over the use of ritodrine given the marked maternal side effects of the latter. Therefore, even if the protocol had been

[48] There is a reading list attached to the 1997 protocol. Mr Hare said this was a skeletal list. If writing a protocol a consultant should fully acquaint himself or herself with the literature.

available and it suggested that ritodrine should be used, I consider that it would have been outdated and nifedipine should have been administered as was widely undertaken at the time…..

(c) Despite the fact that the Defendant was not part of (or conducting its own) clinical trial

…….

Atosiban was not licenced until 2000 so this was not a viable alternative. It follows that the only alternatives in 1995 were to give ritodrine (associated with marked side effects), nifedipine (which required further evaluation), or no treatment which was considered (and still considered by some) not to be ethical. Thus, nidfedipine was the only sensible option at the time despite there being no high quality evidence of efficacy or improved outcomes…

(d) (ii) Failed, negligently and in breach of the 1997 Protocol, to start an intravenous infusion running before instituting Nifedipine treatment….

…..

In 1995 it was considered that maternal fluids were relatively contraindicated in preterm labour. This was because ritdorine was falling into disrepute and there had been a number of serious maternal side effects (including maternal deaths) reported. It was considered that this was in part due to pulmonary oedema which was exacerbated by administration of maternal fluids…."

105. It was put to Professor Thornton in cross-examination that (a) he was suggesting in the report that Nifedipine was the only sensible option, (b) he was exaggerating by saying that in effect Ritodrine had been supplanted by Nifedipine by the mid-1990s. His response was that Ritodrine was falling into disrepute[49], but that in 1995 Ritodrine was a reasonable treatment to use, though Nifedipine had been introduced into a number of units at that time. Ritodrine was not universally in disrepute by 1995, but by the end of the decade it was. In the earlier sections of his report[50] he talked about the history and difficulties of Nifedipine, the later extracts were from sections dealing with Mrs Harris' treatment. In the Defendant's unit in 1995 Nifedipine was the choice. What could not happen was that different drugs would be used by different consultants and registrars in the same unit. There needed to be conformity of treatment in a unit. This was important to reduce the risk of mistakes. Nationally it was reasonable to use a number of drugs in late 1995.

106. Some sections of Professor Thornton's report might be understood to be suggesting that Ritodrine should not have been used in 1995. However, that was not what he said he had meant. Also, that might reflect his personal view of the how he perceived matters, given that he is likely to have been in the avant garde. His oral evidence in summary was that both Ritodrine and Nifedipine were acceptable tocolytics to use as at 1995. That fits with a statement in paragraph 11 of his report where he says: "The timing of this trial[51] indicates that there was clinical equipoise of the use of nifedipine and

[49] He relied on the RCOG 1994 Guidelines (Item 10) in support of this
[50] On the above extracts up to and including the 'General Comments on case'
[51] 1992-1995

ritodrine at that time". I therefore do not accept any substantial criticism of Professor Thornton in this regard.

Review of the literature

107. For the sake of clarity I have set out in the Appendix to this judgment, relevant extracts from the literature adduced in evidence. It is there itemised and referenced. In the body of the judgment I will refer to a piece of literature by its item number in the Appendix.

108. In the 1980s, because of increasing concern about the side effects of Ritodrine, (the then [and still] only drug licensed for tocolysis), new drugs, including Nifedipine, were receiving clinical evaluation. There were also concerns about the efficacy of Ritodrine. Two United States papers (items 1 & 2) discussed these issues and the 1990 review paper (item 2) said that calcium channel blocking agents represented an apparently powerful class of tocolytic drugs, though concern over their effect on the fetus and newborn[52], as well as their unproven efficacy, should limit their clinical use pending further investigation.[53]

109. Item 3 (1991) compared Nifedipine and Ritrodine. Mr Hare said this was an interesting contribution to the debate, but did not accept that this one small trial demonstrated progress, nor that studies were increasingly supporting Nifedipine in preference to Ritodrine.

110. In July 1992 a paper was published in the New England Journal of Medicine by the Canadian Pre-term Labor Investigators Group. This indicated that Ritodrine had no beneficial effects on perinatal mortality but was associated with increased maternal morbidity – particularly the potential to cause pulmonary oedema in the mother. Shortly after this publication a further two fatal cases of complications related to pulmonary oedema were reported by the Committee on Safety of Medicines (CSM)[54]

111. Mr Hare accepted that the New England Journal of Medicine is a pre-eminent Journal and that this was an important article. Mr Hare further accepted that, although Ritodrine was still in the textbooks and Nifedipine was not, there was an increasing opinion that Nifedipione needed to be investigated. His opinion was that there was an increasing feeling among specialists in tocolysis that Nifedipine might be, not was, a reasonable alternative. He said that the research basis was not nearly adequate.

112. In December 1993 an article (Item 5) was published in the British Journal of Obstetrics and Gynaecology. It did not suggest further research and strongly suggested that Nifedipine could be used as tocolysis. Its conclusion is that Nifedipine is as effective as Ritodrine in suppressing preterm labour and its use is associated with less frequent side effects. This journal is the one most commonly read by obstetricians in the UK and has what is described as a 'high impact factor' as a journal. Mr Hare believes that the article contains a number of flaws, but he accepted that a reasonable clinician reading

[52] Based on animal, not human, studies.
[53] The statement that there were no randomized clinical studied to confirm their efficacy remains the case even today. Despite that, they have been recommended for use by the Royal College of Obstetricians and Gynaecologists since 2002 and by NICE since 2015.
[54] This is taken from the Introduction to the 1994 RCOG Guidleines (Item 10 in the Appendix). See also the Historical Perspective set out in Item 4 of the Appendix.

this article in a a well-respected journal, absent a subsequent paper seriously undermining it - which there was not - would be entitled to rely on it.

113. In April 1994 a further article (Item 6) was published in the journal Obstetrics and Gynaecology. This is one of the two most respected American journals, with a very high impact factor. It is a review article, relying on and bringing together the evidence from 90 references. In his report Mr Hare had described the article as poorly written and over optimistic. This included 3 criticisms: In summary: (a) the previously published trials are dealt with in simplified form; (b) the paper wrongly combined evidence from the use of Nifedipine in the treatment of pregnancy induced hypotension with that from its use in normotensive women in preterm labour, so as to provide evidence of its safety for mother and fetus, and (c) it underplayed the significance of the danger to the fetus from animal experiments, attributing this to anaesthesia, poor hydration and dose disparity. Mr Hare's opinion was that, notwithstanding this paper, and previous papers, Nifedipine should still have been regarded as an untried drug and should not have been in use.

114. Nevertheless, Mr Hare accepted that the concession he made about a reasonable clinician reading this journal at the time[55] was applicable. In this paper, also, there has been no subsequent literature seriously undermining its conclusions. The implication of this article is that a reasonable body of clinicians in 1995 could use Nifedipine as tocolysis.

115. Item 7 is a paper written in 1997 by Papatsonis et al. It was suggested to Mr Hare that Papatsonis is a leading authority in the field. Mr Hare said he had come under criticism and that the (subsequent) Cochrane review in which he was involved had come under criticism because Papatsonis was a researcher. Mr Hare had not referred to Item 7 in his report. He said he did not consider a 1997 paper relevant to the position in 1995. It was pointed out that in paragraph 34 of his report, he had referred to later opinions and advice on Nifedipine, stating: "There is still controversy concerning the use of the drug." He said he did not refer to it there as it was a research paper, not a review paper; he had referred to the Cochrane review.

116. Mr Hare said that he was aware that Item 7 was the largest ever study comparing Ritodrine and Nifedipine. The study compared patients in 3 hospitals in Holland between February 1992 and February 1995. All patients in the trial were given Nifedipine. It interpreted the literature as Nifedipine having fewer side effects than Ritodrine and concurred with this.

117. In his 2nd report, commenting on Item 7, to which Professor Thornton had referred, Mr Hare said that he could not accept that "obstetricians working in an English District General Hospital in 1995 should base their practice on a research project that has just been completed in two hospitals in the Netherlands and has yet to be published". He said in evidence that when he wrote this, he thought it possible that other reputable hospitals in the UK and US were using Nifedipine, but he did not know. It was put to him that, apart from Musgrove Park and Walsgrave Hospital in Coventry, a hospital in Denver was using it. He said that if that was the case, it was relevant but did not make it correct.

[55] As recorded in the paragraph of this judgment relating to Item 5.

118. In his reports Mr Hare had relied upon two textbooks for the position relating to prescribing tocolysis in the mid-1990s. These were Dewhurst (fifth edition 1995 - Item 8) and Turnbull (second edition 1995 - Item 9). Mr Hare agreed in cross-examination that textbooks can lag behind the latest research. The section in Dewhurst on Ritodrine is out of date, the last date of any literature referred to is 1978. There is no reference to any of the literature on Nifedipine which had been produced during the 1980s and early 1990s. Turnbull refers to some of the more recent literature after 1990 on Nifedipine. It concludes: "Its use should be confined to appropriate trials at present but its apparent safety justifies continuing investigation."[56] Mr Hare disagreed with the suggestion that Turnbull was out of date by 1995 in saying this, the basis of the suggestion being that there is no reference to literature post 1990.

119. In 1994 the RCOG produced Guidelines on the use of Ritodrine (Item 10). This followed the Canadian Pre-term Labor Investigators Group Study and two reported fatal cases of complications related to pulmonary oedema. These Guidelines discuss only Ritodrine[57]. There is no discussion of other groups of drugs (e.g. Nifedipine) which might be used to inhibit pre-term labour. Mr Hare said that RCOG Guidelines are very highly thought of and generally accepted as policies. He said they should be available on every ward. Professor Thornton said that this document was a warning about the use of Ritodrine, as the Introduction makes clear. It was not a review of all possible tocolytic drugs.

120. The Drug and Therapeutics Bulletin (1992 - Item 11) gave examples of when unlicensed use of drugs would seem justified. These included where (a) the licensed indications do not reflect current knowledge, (b) the indications listed do not include well proven uses of the drug and (c) the licensed indications are over restrictive.[58]

121. Another textbook, Enkin et al., (1995 - Item 12) says there are not enough data on Nifedipine to justify its use outside the context of well-designed and carefully monitored randomised trials. Mr Hare endorsed this viewpoint, despite that fact that there is no reference in the textbook to any of the literature on Nifedipine in the book. He said it was a guide, a summary. Mr Hare was asked what a doctor who had read (i) the literature in high quality journals that Nifedipine was recommended and (ii) the summary in Enkin should do. He said the doctor should rely on evidence-based medicine.

122. In 1997 the RCOG published another Guideline on Beta-Agonists (Item 13). It made a reference to calcium antagonists as 'adjuncts to beta-agonists' and said that they had not been shown to have the desired effects and that the available data did not justify their use. The only reference for this statement was Enkin et al. (Item 12). According to Professor Thornton, what was being there discussed was Nifedipine in addition to Ritodrine, the desired effect being to attempt to reduce cardiovascular side effects. This, he said, is a completely different situation from evaluating the advantages/disadvantages of the two drugs as tocolytics.

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[56] Earlier it seems to suggest that it is in current use: "Current drugs used are beta-mimetics….calcium channel blockers…"

[57] It says that the comments in the Guidelines could be deemed to be other beta-agonists

[58] It must be appreciated that Nifedipine is still unlicensed as a tocolytic but has been recommended for that use by the RCOG since 2002 and NICE since 2015. (See later in the judgment).

Post 1995 Literature

123. The RCOG 2002 Clinical Guideline (Item 14) acknowledges the use of Nifedipine[59]. Although it questions the evidence base for substantive benefit for the baby from tocolysis, if a tocolytic agent is used Nifedipine is suggested as preferable to Ritodrine. Mr Hare said that by 2002 the use of Nifedipine was creeping in and that the responsibility for the prescription of it was down to the prescribing doctor. However Item 14 describes it as one of the drugs "in current use", while saying that it is likely that Ritodrine "remains the most widely used". This is strongly suggestive that there was not insubstantial use of Nifedipine by 2002.

124. In 2013 the GMC published Guidelines (which did not exist in 1995) on prescribing unlicensed medicines. Extracts are set out in the Appendix, at Item 15.

The RCOG Yearbook 1995 – Item 16

125. According to Mr Hare, the RCOG Yearbook is a vehicle for publishing major literature in the preceding year and developments in practice. The Yearbook is marketed principally at consultants. Professor Thornton was cross-examined about a section in the 1995 Yearbook (Item 16) of which he was a co-author. It was put to him that what he said in that document was the polar opposite of his report[60]. He disagreed and made the following points:

- He said that the document was a summary of the situation at that time. It reflected the fact that the RCOG was not recommending the use of Nifedipine at the time, but that it was accepted in many units. He was giving the pros and cons of all drugs and really asking clinicians to review the use of Nifedipine. He was discussing the drugs and how they worked. He added that we still do not have proper trials for Nifedipine. He was trying to encourage those trials before a change in clinical practice.

- He was not writing a guideline. It was not his place to recommend any particular treatment. He did not say it was reasonable to use Nifedipine because he was not making a recommendation. Nor did he reference any papers recommending the use of Nifedipine. He would expect doctors to obtain information as to whether or not to use one or the other drug by reading papers, attending conferences etc. District General Hospitals would take their lead from tertiary referral centres.

- At the time he was a Senior Registrar. He would not want to put his name to any specific treatment. At that stage he was much more interested in the basic science than clinical practice. However, it is clear from the Yearbook that Nifedipine had been used.

126. In re-examination Professor Thornton was asked what an obstetrician should do in 1995 faced with the evidence, including the yearbook and two new pieces of literature (items 5 and 6) recently published in high impact journals. His response was that an obstetrician reading the Yearbook would know that Nifedipine was not recommended

[59] And another tocolytic drug, Atosiban
[60] The relevant extracts are in the Appendix.

by the RCOG or licensed. However, from the papers it would be apparent that Nifedipine was as effective as Ritodrine and was not associated with its side effects.

Professor Thornton's evidence as to the use of Nifedipine in 1995

127. In his report Professor Thornton had asserted that the administration of Nifedipine was widely undertaken in 1995. In evidence he said that he was in Cambridge in 1995. Cambridge was using Ritodrine. He described Cambridge as tending to be very conservative. His feeling was that in 1995 others were using Nifedipine. A proportion of units did favour Nifedipine in 1995. This was partly based on his retrospective analysis. That was his recollection and he regarded the use of Nifedipine at that point as being entirely reasonable.

128. The 1997 Defendant's Protocol, written by Mr Fox and Mrs O'Sullivan said Nifedipine was as good as any other agent and was probably the safest drug for mother and baby. The reading list included the 1994 RCOG Guidelines and Kupferminc et al. (Item 5)[61]

129. When Professor Thornton moved from Cambridge to Coventry in 1998, Coventry was using Nifedipine as a tocolytic. By 2005 53% of hospitals were using Nifedipine, 40% used Atosiban and Ritodrine was being phased out.[62]

Discussion

130. An important preliminary point is that the RCOG 1994 Guidelines (Item 10) and the 1997 Guideline (Item 13) both contain an endorsement in essentially the same terms. The endorsement is:

> "These guidelines were produced under the direction of the Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists as an educational aid to obstetricians and gynaecologists. These guidelines do not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognised methods and techniques of clinical practice for consideration by obstetricians/gynaecologists for incorporation in to their practices. Variations of practice taking into account the needs of the individual patient, resources and limitations unique to the institution or type of practice may be appropriate"

> This endorsement may properly be taken as some support for Professor Thornton's view that the 1994 and 1997 Guidelines were limited in their intended remit. Their purpose was not to evaluate different tocolytics, much less to recommend a course of treatment i.e Ritodrine over Nifedipine.

131. Mr Hare accepted that it was reasonable to offer Nifedipine after the publication of Item 14 in 2002, though in the joint statement he added: "Many consider that the recommendation for the use of Nifedipine remains on inadequate evidence, especially with regard to safety." He said that if the doctor is satisfied of the advantage of Nifedipine over Ritodrine, then it is not negligent to prescribe Nifedipine, having told

[61] Item 5 is the BJOG paper. The reading list also included a 1990 American paper by Ferguson et al, not produced in court but referred to in other articles in the Appendix, namely Items 5, 7 and 9. It was entitled: *A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome.*

[62] See letter referring to UK survey. Johnson & Mason BJOG 112, pp 1582-1584

the patient that it is an unlicensed drug and giving the patient a proper explanation. He said that there are still no double-blind high quality trials on Nifedipine.

132. Mr Hare agreed that the safety profile of Nifedipine had not changed since 1995 but said that doctors pay attention to authoritative Guidelines. In 2015 the NICE Guidelines recommended the use of Nifedipine as the first choice for tocolysis. Mr Hare said that NICE was written taking account of all considerations, including the cost of Nifedipine. His opinion was that, if the economics of Nifedipine were not taken into account, he did not think that NICE should recommend Nifedipine.

133. As to prescribing an unlicensed drug[63], Mr Hare said that if it is given by a reasonable body of practitioners, it would need a consultant's authority and would depend on whether there is a reasonable alternative that is licensed.

134. Mr Hare did not think that, even now, a doctor writing a Protocol on tocolysis should be suggesting Nifedipine. He said that no doctor, having informed him/herself of the research should write Nifedipine into such a Protocol. That is consistent with his view that the underlying research has not changed over the last 20+ years.

135. What therefore are the conclusions which the Court draws from this expert evidence? They are these:

(i) Mr Hare and Professor Thornton are both obstetricians who acted in good faith. Both are responsible, competent and respectable experts. Is the evidence of both of them logical and reasonable?

(ii) It is fair to say that they approach the issue from different standpoints. Mr Hare gave the impression that he was more conservative, Professor Thornton more prepared to be avant garde, in approach. This may reflect the fact that Mr Hare was a consultant in a District General Hospital. He has not published or carried out any research into tocolysis. Professor Thornton has spent much of his life researching the subject and working in a teaching hospital. What is troubling is that, despite the recommendation from the RCOG since 2002, and NICE since 2015[64], Mr Hare still does not believe that Nifedipine should be prescribed. This is internally consistent with his opinion that Nifedipine was not proven to be safe in 1995 and is not proved to be safe now, there having been no high quality double-blind studies. However, on the evidence available to me it seems much more probable that Nifedipine is now properly regarded as a safe tocolytic and therefore could properly have been regarded as such in 1995.

(iii) An unusual feature of this case is that it is common ground that by 2002 at the latest it would not have been negligent to prescribe Nifedipine in preference to Ritodrine. In clinical negligence cases the question is often whether a clinician kept up with advancements in treatment/knowledge, and whether s/he should be held in breach of duty for seeing matters through the eyes of a clinicians at the time of the alleged negligence. This case is the opposite. The question in effect is whether the clinicians were ahead of their time in prescribing a drug about which it is alleged insufficient was known to prescribe it in late 1995, but which, seen through the eyes of clinicians from

[63] Nifedipine is still unlicensed for use as a tocolytic

[64] It is always a possibility that he will be shown to be correct and the RCOG and NICE to be wrong. However, I have to work on the quality of the evidence available to me at this point in time.

(at least) 2002 onwards, would have been an entirely appropriate treatment. This is despite the fact that then, as now, it remains unlicensed for the purpose for which it is used and there have still been no convincing double-blind studies or further primary research. Though the claim, when so analysed, may seem strange, yet it is an entirely logical proposition. I shall consider the claim by looking at the state of knowledge in November 1995[65].

(iv) When considering the expert evidence I remind myself in particular of the comments of Green J in *C v North Cumbria University Hospitals NHS Trust* at [25(vii)], namely that a Judge should not just accept an expert opinion; it should be tested both against the other evidence tendered during the course of the trial, and against its internal consistency. If the evidence is from a person of real experience, exhibiting competence and respectability, and it is consistent with the surrounding evidence and internally logical, a judge should attach considerable weight to it.

(v) Nifedipine was unlicensed for tocolytic use in 1995. It is still unlicensed in 2019. Nevertheless, the 2002 RCOG Clinical Guidance (Item 14) and the NICE Guidelines recommend its use. In the former it is described as preferable to Ritodrine. In the latter "Full Guideline" on "Preterm labour and birth", some 60 pages are devoted to tocolysis. In the recommendations it is said that Nifedipine should be considered/offered to women between 26 and 33+6 weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour. As to Ritodrine (a betamimetic) it says: "Do not offer betamimetics" for tocolysis. There are many reasons why a drug may remain unlicensed for a particular use. Regards must nowadays be had to the GMC Guidance of 2013 (Item 15). Nevertheless the fact that Nifedipine was unlicensed is merely one factor, and I find, not a strong factor, in the light of the other evidence.

136. I was taken to 5 particular papers between 1988 and 1994 (Items 1-3, 5-6). There were a number of other pre-1995 papers in the bundles to which I was not taken.

137. The 5 papers show:

- An increasing, though initially guarded, endorsement of the use of Nifedipine.
- Real concerns about the side effects of Ritodrine. These were highlighted and reinforced by the Canadian evidence, and the two subsequent deaths, which are reported in Item 10.

138. Items 5 and 6 in 1993 and 1994 respectively[66] represent a much more positive basis for prescribing Nifedipine compared to Ritodrine. They were in highly respected journals. Certainly, although Mr Hare criticised Item 5 in particular, his evidence was that he was not aware of anything which has been published which demonstrates that they have been seriously undermined[67]. Item 5 is a research paper. It of course has a limited number of participants in the study, but it is an important part of a continuing and progressing picture. Item 6 is a review paper. It collates and assesses 90 references, the substantial body of literature on calcium channel blockers at the time.

[65] Though see Epilogue to this judgment
[66] Both Item 6 and the 1994 RCOG document (Item 10) were published in April 1994
[67] Indeed as time progressed, the viewpoint became the one endorsed by the RCOG and NICE>

139. I have already dealt above with Item 10 and why that cannot be regarded as evaluating different tocolytics or recommending Ritodrine over Nifedipine. As to Item 16, Professor Thornton's 1995 Yearbook says, for example:

- While cautious about Ritodrine and its side-effects, it is the only licensed drug and is an effective tocolytic

- Calcium channel blockers may be associated with adverse fetal effects and it is important not to abandon existing drugs before the risks and benefits of new drugs are fully determined

140. I take into account what Professor Thornton said in evidence about Item 16. I accept what he says. In my judgment he was, as a then Senior Registrar, setting out the conservative viewpoint rather than the avant garde or 'cutting edge' viewpoint. He does not mention the recent literature on Nifedipine. His task in writing was not to advocate change. At that time he was at Cambridge where the consultants supervising him still used Ritodrine. He described Cambridge as 'very conservative'. Item 16 does not negate a contention that a responsible body of obstetricians was using Nifedipine in 1995.

141. In my judgment, the literature as at April 1994 was such that it would be wrong to say that practitioners who sought to use tocolysis would be in breach of their duty of care.

142. What evidence is there of practitioners using Nifedipine in 1995? The answer is that there is relatively little. It does not follow from this that only a tiny minority was doing so. Over 20 years have passed, there are no extant surveys and no wide-ranging documentation from other hospitals. The 2002 RCOG Guidelines (Item 14), before recommending the use of Nifedipine over Ritodrine, says: "There is little reliable information about current clinical practice but it is likely that Ritiodrine hydrochloride..remains most widely used." There was a sort of survey which led to the letter in the BJOG that by 2005 53% of hospitals were using Nifedipine, but that was after the 2002 RCOG Guidance, so tells us nothing about 1995. It is simply not known whether very few or a substantial minority of hospitals were then doing so. The only evidence we have about 1995 is:

(i) the Defendant was using Nifedipine as the tocolytic of choice

(ii) Mr Bidgood's recollection in 2010[68] was that *"..my memory is that this was a recipe for the dosage and regimen based on the experience of staff working in Bristol and using their Protocol as a guide….in those days we were still using guides based on the local hospital handbooks and the practice as far as I remember it was that most of the doctors having worked in Bristol used the Bristol Handbook. I had provided access to the St Mary's[69] Handbook and also the Bristol one which was available on the delivery suite. This was not a formal guideline or protocol in the sense that we follow now but provided a commentary and recipe for the management of things like preterm labour".*

[68] Letter 6 September 2010

[69] In submissions Mr Moon QC said he had been told that there were two St. Mary's obstetric hospitals, one in London (Paddington) and one in Manchester. His instructions were that Mr Bidgood had previously worked in the London St Mary's. [This is not in evidence].

(iii) In the Netherlands (Item 7) 3 hospitals used nifedipine between February 1002 and February 1995, the results of which were published in 1997

(iv) In 1987 Nifedipine "was introduced as an alternative tocolytic agent…at St Joseph's Hospital", Denver, Colorado[70], In the light of concerns raised by some animal studies a systematic review of all patients was undertaken of 102 patients. The conclusion was: "Nifedipine was a well-tolerated and safe tocolytic in this population and warrants further investigation".

143. Thus, after this period of time there are some pieces of evidence from recollection and from the literature that Nifedipine was being used in the UK, the USA and the Netherlands before and during 1995.

144. In addition there was Professor Thornton's recollection. It is difficult to give great weight to that, but it is in line with the fact that a number of hospitals were then administering Nifedipine as a tocolytic.

145. Taking the evidence as a whole, and weighing the risks and benefits of using Nifedipine as they were known in 1995, Professor Thornton's opinion is eminently defensible on this point. It has also been borne out by subsequent events such that Nifedipine is now the drug of choice for tocolysis, despite the lack of any further hard primary research. It was also borne out by the 1997 paper (Item 7) which reference 8 papers which were from 1995 or earlier for the proposition that:

"Studies comparing ritodrine with nifedipine in the management of preterm labour suggest a similar tocolytic efficacy but fewer maternal side effects and no adverse fetal side effects with nifedipine."

This large-scale study then examined this finding, effectively corroborated it and found other advantages of Nifedipine over Ritodrine.

146. For those reasons it was not a breach of the duty of care to prescribe Nifedipine as a tocolytic in 1995.

Administration of Nifedipine

147. There had been an allegation that it was negligent for Mrs Harris to have been given Nifedipine sublingually, rather than orally. However, there were a number of references in the literature of this practice. Mr Hare accepted that, if it was reasonable to prescribe Nifedipine, then it was not a breach of duty to have administered it sublingually.

Intravenous Infusion

148. In the 1997 Protocol, the Nifedipine Regimen requires: "Site a venflon and start infusion of Hartmann's solution." It is not known what any 1995 Protocol required. Doctor Bett said she would have followed the requirements of a Protocol.

149. In his 1st report, Mr Hare acknowledged that, though in some of the studies setting up an i/v infusion was thought to be a necessary prelude, it is not mentioned in others. His

[70] Murray et al: Nifedipine for Treatment of preterm labor: A historic prospective study." Am J Obstet Gynecol 1992; 167:52-6

view is that, given the acknowledged risk of maternal hypotension which would normally be treated by immediate and rapid infusion of intravenous fluid, this precaution would seem to be mandatory.

150. In evidence Mr Hare said that the incidence of hypotension is reported as high as 40%. Therefore, not to have the precaution of i/v infusion should hypotension occur is unacceptable. He accepted that the 2015 NICE Guidelines do not require an i/v infusion to be set up. He did not know why this was the case.

151. It was clarified that there was no separate allegation that, if i/v infusion had not been set up prior to administration of Nifedipine[71], then it should have been set up later. Mr Hare said that, though he thought that should be done, the beneficial effect would have been minimal.

152. Professor Thornton said that he disagreed with the 1997 Protocol in suggesting that a cannula should be put in advance into a woman with threatened preterm labour. A cannula should not be put into a vein unless there is a good reason to do so. He said that if hypotension followed a dose of Nifedipine, the first response should be to lift up the woman's legs. If there was real concern, then it would not be unreasonable to put up an i/v line and start fluids. In Mrs Harris' case he would not have been concerned if the blood pressure fall was Nifedipine related. The fall had been only for a minute or so and was not much of a fall.

153. There is therefore conflicting evidence from Mr Hare and Professor Thornton on this issue. On the basis of Professor Thornton's evidence, which is logical and consistent with surrounding evidence – e.g. the 2015 NICE Guidance and a number of respectable studies – I do not find that there was any breach of duty on this basis. I find that a reasonable body of clinicians would not have set up an i/v line prior to the administration of Nifedipine.

The second dose of Nifedipine

154. Mr Hare's evidence as to whether a 2nd dose of a tocolytic drug was indicated depended entirely on the evidence on contractions. If, contrary to his opinion, the midwife's examination at 0120 demonstrated continuing contractions, then it was reasonable to give a 2nd dose. Professor Thornton said that once the regime for administration had started, a doctor would follow the Protocol. Protocols differed. The key question was whether it was justified to start tocolysis. In order to start it, he would expect there to have to be contractions. If contractions continued it would be reasonable to give a 2nd dose. If they did not continue, since the initial dose was a relatively small dose of 10mg, there would be no hard line that a 2nd dose should not be given. In any event, although he accepted that at 0120, it does not suggest that Mrs Harris' abdomen was palpated again, Professor Thornton's understanding of the note which refers to her abdomen being painful "in waves", was that Mrs Harris was still complaining of contractions before the 2nd dose was given at 0135[72].

[71] And it was not negligent to fail to do so

[72] That is also how both Doctor Bett and Mr Emovon interpreted the note – see above.

155. Doctor Bett said she would have written in the drug sheet "If contractions cease then no further Nifedipine", as that is what the Protocol must have said[73]. I accept that.

156. I find on both grounds for the Defendant on this issue. That is to say:

(i) Although Mrs Harris' abdomen was probably not palpated at 0120, on the balance of probabilities she was complaining of continuing contractions. This is based on the fact that she complained of her abdomen still being painful in waves. If the contractions had stopped, then it can properly be inferred that the midwife would have followed Doctor Bett's instruction – see previously in this judgment.

(ii) In any event, I accept Professor Thornton's evidence that, even if the contractions had ceased, it was reasonable to give a second dose in the circumstances obtaining. This is notwithstanding that the Protocol probably recommended against another dose.

Summary

157. (1) It was reasonable for Doctor Bett to diagnose, as she did, that Mrs Harris was in threatened preterm labour. It was therefore reasonable to prescribe tocolysis

(2) There was no breach of duty in prescribing Nifedipine in 1995

(3) Failure to set up intravenous infusion prior to administration of Nifedipine was not a breach of duty

(4) The administration of a second dose of Nifedipine was not a breach of duty

158. In summary, the Claimant has not proved any breach of duty on the part of the Defendant and the claim must therefore fail.

Epilogue

159. I have previously stated in this judgment that I shall try the issue of the prescription of Nifedipine as a tocolytic drug by the standards of November 1995, not subsequently. This accords with the traditionally understanding of the authorities. On that basis I have found for the Defendant. However, there were brief submissions by Mr Moon QC that there is nothing in the *Bolitho* test that requires me to do this. If a doctor who would have been held liable in 1995 for breach of duty in prescribing a drug whose use was not accepted as appropriate by a responsible body of practitioners is subsequently vindicated, such that a doctor prescribing the same drug in 2002 would not be in breach of duty because of changes of opinion in the profession, should the 1995 doctor be held to be negligent in a trial taking place after 2002? The point has not seemingly arisen before. Mr Sweeting QC submitted that a Claimant is entitled to be treated by reference to the standards at the time of treatment.

160. It is not necessary for me to decide the point and I do not do so, leaving it for consideration of a higher court if and when it arises.

---

[73] The 1997 Protocol is not so stark or clear in its recommendation. It says: "If contractions reduce substantially repeat Nifedipine..."

Appendix

Item 1

Nifedipine versus Ritodrine for suppressing preterm labor. Meyer et al. 1988 The Journal of Reproductive Medicine.

> "Fifty eight women in preterm labor were selected randomly to receive either oral nifedipine or intravenous ritodrine hydrochloride. In comparison to ritodrine, nifedipine had similar tocolyltic efficacy with fewer adverse maternal and fetal side effects … Preliminary data suggest that nifedipine is a safe, effective and well-tolerated tocolytic agent. It may prove to be a suitable alternative to ritodrine hydrochloride, especially for women in whom beta-sympathomimetics are contraindicated.
>
> **Introduction**
>
> …
>
> The efficacy of sympathomimetics, including Ritodrine hydrochloride, is generally well accepted, yet the potential side effects have lessened enthusiasm for its use. Currently, interest centres on the tocolytic use of calcium channel blockers. The aim of the present investigation was to compare the tocolytic efficacy and safety of nifedipine and ritodrine hydrochloride.
>
> …
>
> **Results**
>
> Between August 1986 and February 1987, 34 women were randomly selected to receive nifedipine, while 24 received ritodrine hydrochloride …
>
> **Conclusion**
>
> Our study lent support to the clinical use of nifedipine for preterm labor. In comparison to ritodrine hydrochloride, nifedipine demonstrated similar tocolytic efficacy with less severe maternal side effects and metabolic alterations. Fetal homeostasis as measured by external fetal monitoring … appeared unaltered. Prematurity, with its inherent dangers, seems a much greater risk to the fetus than does nifedipine tocolysis."

Item 2

The safety and efficacy of Tocolytic Agents for the treatments of preterm labor: Besinger and Niebyl. Obstetrical and Gynaecological survey 1990, by Williams and Wilkins (USA) Vol 45 No. 7, page 415.

"… a diverse variety of tocolytic medications have been proposed for clinical use, with betamimetics and magnesium sulphate being the common therapeutic agents of choice in the United States today. The clinician using these agents should be aware of the significant maternal and fetal side effects associated with these particular medications. New classes of pharmacological agents, including … calcium channel blockers … have been proposed as tocolytic agents and are currently undergoing critical evaluation. The purpose of this review is to provide a compilation of the available clinical studies that document the safety and efficacy of these various tocolytic agents.

…

In 1980 the United States Food and Drug Administration approved Ritodrine hydrochloride … for inhibition of preterm labor. Among all the tocolytic agents to be discussed in this article, this is the only one so approved and the other agents should be considered experimental. However, the use of approved drugs for nonlabelled indications may be entirely appropriate based on medical advances extensively reported in the medical literature … the purpose of this article is to provide a compilation of the available clinical studies that document the efficacy and safety of these various tocolytic agents

…

Beta-Adrenergic Agonists[74]

…

The intravenous administration of betamimetic agents can stimulate beta-receptors in multiple organ systems and is responsible for the various clinically significant side effects associated with these medications (33). Maternal cardiovascular side effects are most frequently seen with beta-adrenergic agonists, including hypotension, tachycardia, and arrhythmia.

…

As the clinical use of beta-adrenergic agonists has become more widespread, more than 80 cases of pulmonary edema have been reported in the literature (39, 51-70). This life-threatening complication has been reported in up to 5% of patients receiving intravenous betamimetic therapy (35, 39).

…

[74] This includes Ritodrine.

> Several maternal deaths have been associated with administration of betamimetic therapy (57, 77, 78). While most of these maternal debts were not directly attributable to the drug, a majority of these patients had a history of cardiac disease or pulmonary hypertension, pointing out the importance of pre-treatment screening for cardiopulmonary disease.
>
> …
>
> A more recent multicentre European study of 99 patients randomised to receive either intramuscular Ritodrine or placebo followed by oral therapy did not show long term efficacy … these more recent studies raise serious questions regarding the efficacy of Ritodrine in the treatment of preterm labor.
>
> ……..
>
> Oral maintenance therapy with Ritrodrine appears to be successful in preventing recurrent preterm labor. In one randomised double-blind study of oral maintenance therapy with Ritodrine, 70 patients were initially treated intramuscularly with Ritodrine and 59 patients received successful tocolysis beyond 24 hours …
>
> *Calcium Channel Blocking Agents*
>
> …
>
> The clinical experience in the treatment of preterm labor with this group of tocolytic agents has been limited. To date, no controlled, randomised clinical studies have been reported to confirm the efficacy of these tocolytic agents …
>
> The major concern restricting the clinical use of calcium channel blocking agents is the effect upon uteroplacental blood flow[75] … In the 65 patients who have received Nifedipine during pregnancy, no adverse fetal or neonatal side effects have been described …
>
> In summary, calcium channel blocking agents represent an apparently powerful class of tocolytic drugs. However, the concern over their effect upon the fetus and newborn, as well as their unproven efficacy, should limit the clinical use of these agents pending further investigation.
>
> **Conclusion**
>
> …

[75] There is then reference to some animal studies,

As our clinical experienced with these various medications increases, it becomes readily apparent there is no ideal tocolytic agent available at this time. …"

Item 3

Comparison of Nifedipine and Ritodrine for the Treatment of Preterm Labor. Bracerio et al. American Journal of Perinatology/Volume 8, number 6, November 1991.

"**ABSTRACT**

Treatment of preterm labor with beta-sympathomimetics has been questioned because of the many maternal and fetal complications associated with its use. Nifedipine, a calcium antagonist, has been shown to suppress uterine activity in vitro and in vivo. A randomised prospective study was performed to compare the efficacy of Nifedipine to Ritodrine in the suppression of preterm labor. Data obtained from 42 women, of which 19 were randomised to the Ritodrine group and 23 to the Nifedipine group, were analysed. Ritodrine and Nifedipine were proved to be equally effective in the suppression of perterm labor. However, the Nifedipine group had fewer maternal and fetal complications.

…

There is a need to find a tocolytic agent that is efficacious and has fewer side effects than the agents currently in use. The most widely used agents are beta-sympathomimetics. These agents are associated with several side effects in both mother and fetus …

DISCUSSION

… therefore, calcium antagonists seem ideally suited to suppress premature uterine smooth muscle contractions. On the other hand, the wisdom of using beta-sympathomimetics to treat preterm labor is being questioned. A review article on the treatment of preterm labor includes that the use of Ritodrine should be discouraged because of its questionable efficacy and life-threatening maternal adverse side effects. …

Harake and associates report that on pregnant sheep Nifedipine decreases uterine blood flow and fetal arterial oxygen content. In published human studies there has been no indirect confirmation of Harake's finding in sheep. In our study antepartum fetal heart rate monitoring did not reveal any significant abnormalities…

…

> Most encouraging of all, neonatal RDS[76] and other morbidities were lower in the Nifedipine group, resulting in a significantly lower hospital stay for these infants. Additionally, women who receive Nifedipine experienced fewer subjective and objective drug side effects.
>
> **SUMMARY**
>
> This is a small randomised trial in which both Nifedipine and Ritodrine prove to be effective in suppressing preterm labor. Nifedipine, however, had fewer maternal side effects and less neonatal morbidity."

Item 4

Best Practice in Labour and Delivery, 2nd edition (2016). Chapter 21 The Management of Preterm Labour.

> "Historical perspective
>
> …

In 1982 the Food and Drug Administration approved Ritodrine for use in the USA … There followed a mark increase in pulmonary oedema and in 1986 in the USA and Japan, post marketing surveillance advice recommended the cessation of preloading with intravenous fluids prior to initiation of β_2-agonist treatment. In 1992, the Canadian Preterm Labour Investigators group reported similar findings to the Keirse meta-analysis, namely that β_2-agonists were able to stop contractions and delay delivery for a short time, albeit that they had not been shown to be associated with a reduction in neonatal, mortality or morbidity. In the same issue of the journal, Leveno and Cunningham published an editorial in which they called for a reappraisal of the use of the β_2-agonists. There followed a decline in use of β_2-agonists in the USA and Europe, and in 1999 atosiban was launched in Europe (Austria first). Because of the cost of atosiban, there followed a drift towards the use of cheaper tocolytic alternatives such as magnesium sulphate and calcium channel blockers (CCBs), mainly nifedipine……."

Item 5

Nifedipine versus Ritodrine for Suppression of Preterm Labor. Kupferminc et al. British Journal of Obstetrics and Gynaecology December 1993, vol 100 pp 1090-1094.

> "**ABSTRACT**
>
> **Objective** To compare the efficacy of tocolysis with specific regimens of Nifedipine and Ritodrine. Maternal side effects and neonatal outcome also were evaluated.
>
> **Design** A prospective, randomised trial.

[76] Respiratory Distress Syndrome

Subjects 71 women, including 11 with twin pregnancies, who had uterine contractions and observed cervical changes.

…

Conclusions Nifedipine is as effective as Ritodrine in suppressing preterm labour. Its uses are associated with less frequent side effects.

Preterm delivery is a common obstetric problem. The incidence of preterm delivery is about 7 to 9% of pregnancies, and it accounts for as much as three quarters of the mortality and morbidity among newborns without congenital abnormalities … Therefore major emphasis has been placed on perinatal and neonatal research directed at preventing and lessening the consequences of preterm birth …

The pharmacological choices limited by the number of drugs available and by their safety and side effects, thus necessitating a continuous search for effective drugs with minimal side effects. Currently the most commonly used tocolytic agents are beta-adrenergic drugs, particularly Ritodrine. However, the incidence of troublesome, and occasionally fatal, side effects associated with this drug are of serious concern.

…

There is a growing body of evidence that Nifedipine is effective in suppressing preterm labour with minimal maternal and fetal side effects. In this paper we present the results of a prospective randomised study which was designed to compare the efficacy of oral Nifedipine with our existing regimen for administration of Ritodrine.

…

Discussion

This study shows that Nifedipine is an effective tocolytic agent, comparable to Ritodrine, but it causes fewer side effects and less haemodynamic compromise.

…

Since calcium channel blockers are known to have both a vasodilatory effect and a negative inotropic effect on the myocardium …, haemodynamic side effects are of concern … Ferguson et al … reported a statistically significant increase in maternal heart rate and decrease in both diastolic blood pressure and MAP after sublingual and oral administration of Nifedipine,

> but they considered these changes unlikely to be of physiological importance. Our findings are consistent with theirs. The decrease in blood pressure which we observed after oral administration of Nifedipine, although statistically significant, was unlikely to be of clinical importance and was significantly less than the decrease associated with Ritodrine.
>
> Nifedipine caused an increase in maternal heart rate following each dose, but this was transient and much less pronounced compared with women treated with Ritodrine. Similar observations were reported by Ferguson et al … No significant changes were noted in the fetal heart rate.
>
> Consistent with previous reports (Ulmsten et al 1980, 1984), we found that other side effects associated with oral Nifedipine were trivial, and less common than with Ritodrine even in women who received a 2nd dose of Nifedipine. Treatment with Ritodrine, however, often requires discontinuation due to severe side effects and complications …
>
> We conclude that Nifedipine is a useful tocolytic agent comparable in efficacy to Ritodrine, but with a lower frequency of side effects."

Item 6

Holmes Childress and Katz Obstetrics and Gynaecology, Volume 83, number 4, April 1994, page 616.

> "*Objective:* to review studies and investigations regarding the safety and efficacy of Nifedipine.
>
> *Data sources and methods*: we reviewed the published literature on calcium channel blockers and their pharmacology and therapeutic applications in obstetrics and gynaecology. We paid particular attention to methods of animal research and recent clinical evaluations.
>
> *Conclusions*: the dihydropyridine group of calcium channel blockers … and, specifically, Nifedipine are safe for use in pregnancy. They have little teratogenic[77] or fetotoxic potential. Nifedipine's mechanism of action is through smooth-muscle relaxation secondary to blockage of the slow calcium channels into the cells. In vivo, there is minimal effect on the cardiac conducting system. Multiple studies in women have demonstrated the effectiveness and safety of Nifedipine as an antihypertensive. … Nifedipine is as effective as beta-mimetics in decreasing uterine activity. As a tocolytic agent, it is more

[77] Causative of congenital abnormality.

effective as there are fewer patients who have to discontinue with Nifedipine because of side effects. …

Fetal effects

…

Numerous investigators have reported positively on the fetal and neonatal effects of Nifedipine over prolonged periods during pregnancy. Studies comparing maternal treatment with Nifedipine and other agents have found that fetuses treated with Nifedipine fared at least as well and sometimes better (because of fewer maternal side effects) than fetuses exposed to other medications. Short-term fetal effects from Nifedipine have also been examined. The fetal heart rate during labour, fetal heart rate shortly after maternal ingestion, and umbilical artery Doppler flow studies have not been adversely affected by Nifedipine.

Animal studies have shown varying effects from the dihydropyridine agents. Harake et al, Parisi et al, and Ducsay et al found deleterious effects from high doses of Nifedipine, including declines in fetal arterial oxygen content, acidosis, and fetal deaths in lambs after maternal Nifedipine and Nicardipine treatment. These early reports caused widespread concern among physicians. In contrast, other investigators did not find adverse fetal effects. The contrasting results of animal and human study may be related to maternal haemodynamic effects, changes in the distribution in placental blood (an effect which is unlikely to occur in humans), and the dosages used. Taking all the studies together the large number of women treated with Nifedipine without adverse fetal effects suggests that the animal studies may not be applicable to pregnant women. Nifedipine has not been shown to affect birth weights, even with prolonged fetal exposure. There are fewer studies of Nitrendipine and Nicardipine, but abnormal effects have not been found with these agents, either.

The use of Nifedipine for tocolysis

…….

In all the studies on women, Nifedipine has been as successful as or better than Ritodrine in stopping pre-term contractions. Negative fetal effects have not been found. Long-term use has not been associated with decreased birth weight or neonatal problems. Infants exposed to Nifedipine in utero have shown no untoward effects after one year. Perhaps most important, the maternal side effects have been much worse with Ritodrine, leading to more morbidity and greater discontinuation of the drug. Thus, in summary of the animal and human studies, Nifedipine is an effective agent to decrease uterine contractions,

and because of fewer side effects, it has distinct advantages over current tocolytics."

Item 7

Nifedipine and Ritodrine in the management of pre-term labor: a randomised multicenter trial. Papatsonis et al., Obstetrics and Gynaecology Volume 90(2) August 1997

"Objective: to compare the efficacy of Nifedipine with Ritodrine in the management of preterm labor.

Methods: 185 singleton pregnancies with preterm labour were assigned randomly to either Ritodrine intravenously (*n* = 90) or Nifedipine orally (*n* = 95)…

……..

Conclusion: Nifedipine in comparison with Ritodrine in the management of preterm labour is significantly associated with a longer postponement of delivery, fewer maternal side effects, and fewer admissions to the NICU…

……..

Studies[78] comparing Ritodrine with Nifedipine in the management of preterm labor suggest a similar tocolytic efficacy but fewer maternal side effects and no adverse fetal side effects with Nifedipine …

Discussion

……

Ferguson et al, Meyer et al, and Kupferminc et al all found Nifedipine to be associated with significantly fewer maternal side effects as compared with Ritodrine, and our results concur. The higher efficacy of Nifedipine and the lower incidence of maternal side effects are not the only advantages. The lower neonatal intensive care unit admission rate with Nifedipine is probably the most relevant finding. Nifedipine has the ease of oral administration. Other theoretical advantages are the (relative) lack of influence on maternal cardiac output and carbohydrate metabolism, which is in contrast with the beta-adrenergic agents. In addition, Nifedipine does not interfere with the interpretation of fetal heart rate tracings as does Ritodrine, which may be important in the timely diagnosis of an intra-uterine infection in patients with preterm PROM."

[78] References given are all 1995 or prior.

Item 8

Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates 5th edition, 1995, Chapter 22

> "The early onset of labour
>
> …
>
> Treatment with Ritodrine by intravenous fusion for 24-48h, followed by oral administration for 5-7 days, has been described by Wesselius de Casparis et al. (1971). The drug is now used quite frequently in clinical practice, though its efficacy appears to remain unverified by controlled clinical trials (Hemminki and Starfield 1978; O'Connor et al, 1979). Furthermore, there have been disturbing reports of pulmonary oedema in mothers following its use in conjunction with betamethasone to supress premature labor (Elliot et al, 1978; Tinga & Aarnoudse 1979), and one of Ritodrine-induced acidosis in pregnancy (Desir et al 1978).[79]
>
> …
>
> Calcium agonists such as Nifedipine (probably magnesium sulphate also) are being investigated currently, but only limited data are so far available (Read and Wellby 1986; Odum & Pipkin, 1988). …
>
> …
>
> Probably the beta-adrenoagic tocolytic drugs are the agents most widely used, but they are not without significant risk to the mother in some circumstances, and in most women are associated with unpleasant side effects, including flushing, tremor, headache, sweating and tachycardia. Alternative agents such as prostaglandin inhibitors, calcium antagonists and oxytocin inhibitors, have as yet been insufficiently tested to be introduced into routine use."

Item 9

Turnbull's Obstetrics 2nd edition 1995, Chapter 33. Preterm labour and delivery of the preterm infant

> "**3a. Therapies to improve outcome: delaying delivery**
>
> Several drugs are now available to delay delivery in spontaneous preterm labour and where possible these should be utilised to allow other therapies which may improve outcome to be given. There are few complete contraindications to the inhibition of

[79] There is also discussion of treatment of premature labour with Orciprenaline and Salbutamol.

preterm labour … Current drugs used are betamimetics, prostaglandin synthetase inhibitors, magnesium sulphate, Calcium Channel Blockers and antibiotics.

Beta-Adrenergic Agonists

…

Safety. Maternal side effects of betamimetics are well documented …

Most of the concern over the use of beta-agonists centres on the severe cardiovascular side effects…

The greatest controversy has been reserved for the risk of pulmonary oedema which occurs in 0.3% of cases (Canadian Preterm Labour Investigators Group 1992) … Whatever the cause, the injudicious use of beta-agonists can be lethal and appropriate monitoring needs to be in place…

…

Administration

……..

Beta-agonists should only be used where there is good evidence of preterm labour …

…

Calcium Antagonists

…

Safety. … Severe side effects are extremely rare. Initial concerns over fetal welfare have been largely dispelled (Hanretty et al 1989).

…

Efficacy. Clinical experience is limited with Nifedipine. Trials to date have not been of high quality, and have not demonstrated any benefit over Ritodrine in the prolongation of pregnancy (Bracero et al, 1990; Ferguson et al., 1990; Meyer et al., 1990). It appears well tolerated, and no adverse fetal or neonatal effects have been reported. Its use should be confined to appropriate trials at present but its apparent safety justifies continuing investigation.

Item 10

RCOG April 1994 Guidelines "For The Use of Ritodrine"

"**1. Introduction**

The risk-benefit ratio of Ritodrine hydrochloride …, a beta-agonist licensed to inhibit preterm uterine activity, has been reviewed recently following a series of events. These include the publication in July 1992 of a paper in the New England Journal of Medicine by the Canadian Pre-term Labor Investigators Group that indicated that the drug had no beneficial effects on perinatal mortality but was associated with increased maternal morbidity – particularly the potential to cause pulmonary oedema in the mother. Shortly after this publication a further two fatal cases of complications relating to pulmonary oedema were reported to the Committee on Safety of Medicines (CSM); the pharmaceutical company circulated a letter to doctors reminding them of this side effect and emphasising measures to minimise the risks; and the data sheet has been reviewed and revised.

2. Background

Ritodrine hydrochloride is a beta-agonist … The drug was introduced in the UK in 1974 and has been widely used for the inhibition of preterm labour in the UK, rest of Europe and the USA. …

3. Effectiveness of Ritodrine

The Canadian Pre-term Labour Investigators Group represents the largest placebo-controlled investigation conducted on any tocolytic agent. Seven hundred and eight women were randomised to intravenous Ritodrine … The results indicate that Ritodrine significantly reduced the proportion of women who delivered within 24 and 48 hours after treatment, but there was no significant difference in birth weight or neonatal morbidity overall. …

……

The management of preterm labour will depend upon the cause of the problem (if determined), the gestation and degree of cervical dilatation at presentation, and the availability of neonatal intensive care facilities. The increased likelihood of being able to delay delivery by 24-48 hours by administration of intravenous Ritodrine may allow the possibility of in-utero transfer to a referral centre and facilitate time to administer corticosteroids to promote increased fetal lung maturity…[80]

[80] There is then a discussion about side effects.

Item 11

Drugs and Therapeutics Bulletin, Volume 30, number 25, 7th December 1992: **Prescribing unlicensed drugs or using drugs for unlicensed indications**

> "**Unlicensed use** –
>
> …
>
> ….even when the prescriber is fully aware of the contents of the data sheet there are occasions when non-adherence seems justified, for example where:
>
> • the licensed indications do not reflect current knowledge. The data sheet for prednisolone … recommends that the drug be given in 'divided doses' through the day but clinical evidence strongly favours once daily or even alternate-day dosing.
>
> • the indications do not include well proven uses of a drug. Mountain sickness, a recognised use for acetazolamide, is not mentioned in the data sheet, nor is treatment of dystonia with benzhexol or more recently the use of magnesium sulphate for acute myocardial infarction.
>
> • the licensed indications are over restrictive. Junifen and Brufen syrup both contain 100 milligrams Ibuprofen in 5ml liquid yet for Brufen the indications include use as an anti-inflammatory, and for Junifen as an antipyretic. Brufen costs much less than Junifen, and on cost grounds doctors would be justified in prescribing Brufen syrup for both indications.
>
> Such anomalies may arise if the manufacturer does not wish to alter the product's market niche and/or is unwilling to sponsor the trials necessary to support an application for a licence change."

Item 12

A Guide to Effective Care in Pregnancy and Childbirth, 2nd edition, (1995). Enkin et al.

> "**3 Treatment of active preterm labour.**
>
> ……..
>
> 3.7 *Other drug treatments*
>
> ……..
>
> Apart from trials in which calcium antagonists were used mainly to supplement labour-inhibiting treatment with betamimetic drugs, there have been few attempts to evaluate these agents in preterm labour. There are not enough data on any of these agents

to justify their use outside the context of well-designed and carefully monitored randomised trials."

Item 13

RCOG Guideline January 1997. Beta-agonists for the care of women in preterm labour.

"**1. Introduction**

…

A wide variety of agents have been advocated as suppressing uterine contractions. Currently the most widely used is Ritodrine hydrochloride, a beta-agonist……. The aim of this guideline is to summarise the evidence about the effectiveness of beta-agonists for prevention and treatment of preterm labour and to provide guidance as to how to incorporate this evidence into clinical practice.

2. Evidence from systematic reviews

… Taken together, these studies show that beta-agonists reduce the proportion of deliveries occurring within the first 48 hours after beginning treatment. This is not reflected in any decrease in perinatal mortality or serious morbidity…

3.Risks and side effects

The most common symptoms associated with beta-agonist use are palpitations, tremor, nausea, vomiting, headache and restlessness … Beta-agonists are also associated with hypotension, although this is less of a problem with Ritodrine than some of the earlier agents …

Rare but serious side effects have also been reported following beta-agonist use. These are potentially life threatening and there have been a small number of maternal deaths associated with the use of beta-agonists. Pulmonary oedema is a well-documented complication and most cases are associated with aggressive intravenous hydration. Myocardial ischaemia is another uncommon but serious side effect and is a consequence of the increased cardiac output associated with beta-agonist administration. Women with known cardiac disease should not be given a beta-agonist. Other drugs, such as calcium antagonists and beta blockers, have been tried as adjuncts to beta-agonists in an attempt to reduce the cardiovascular side effects. None have been shown to have the desired effects and the available data do not justify their use…"

Item 14

Royal College of Obstetricians and Gynaecologists Clinical Guideline No. 1(B) October 2002: Tocolytic drugs for women in preterm labour

"1.Purpose and scope

…

A wide variety of agents have been advocated as supressing uterine contractions. Those in current use include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitrous oxide donors and oxytocin receptor antagonists. There is little reliable information about current clinical practice but it is likely that Ritodrine hydrochloride, a beta-agonist, remains the most widely used. …

… The aim of this guideline is to summarise the evidence about the effectiveness of tocolytic drugs for preterm labour and to provide guidance as to how to incorporate this evidence into clinical practice.

…

4.Choice of tocolytic drug

If a tocolytic drug is used, Ritodrine no longer seems the best choice. Atosiban or Nifedipine appear preferable as they have fewer adverse effects and seem to have comparable effectiveness. Atosiban is licensed for this usage in the UK but Nifedipine is not.

…

6. Summary

There is still no clear evidence that tocolytic drugs improve outcome following preterm labour and so it is reasonable not to use them. … There is insufficient evidence for reliable conclusions about more substantive effects on perinatal or infant mortality or on serious neonatal morbidity. It remains plausible that, for selected women such as those who require transfer for neonatal care or time to complete a course of corticosteroids, there may be benefit associated with tocolysis. However, this benefit has not been formally evaluated in randomised trials.

If a tocolytic agent is used, Ritodrine no longer seems the best choice. Alternatives such as Atosiban or Nifedipine appear to have comparable effectiveness in terms of delaying delivery for up to 7 days and are associated with fewer maternal adverse effects. Atosiban is licensed for use as a tocolytic but the purchase price is relatively expensive. Nifedipine is not licensed

for use as a tocolytic and the ideal dosage and formulation are unclear. For both these agents, further evidence is required about their relative effects on substantive outcomes such as neonatal mortality and morbidity, and on safety and long-term outcome for the child.

In view of the current lack of evidence for any substantive benefit for the baby from tocolysis, and the possibility of hazard for the mother, the available evidence should be discussed with the woman and her partner and their preferences taken into account in determining her care."

Item 15

General Medical Council (2013)

"**Prescribing unlicensed medicines**.

……..

68. You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.

69. Prescribing unlicensed medicines may be necessary where:

a) there is no suitably licensed medicine that will meet the patient's need …

70. When prescribing an unlicensed medicine you must:

a) be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy

b) take responsibility for prescribing the medicine and for overseeing the patient's care…

c) …

Information for patients about the licence for their medicines

71. You must give patients … sufficient information about the medicines you propose to prescribe to allow them to make an informed decision."

Item 16

The Yearbook of the Royal College of Obstetricians and Gynaecologists 1995.

*"***The treatment of preterm labour: physiological and clinical considerations**

Steven Thornton and Gerald A Hackett

…

PHARMACOLOGICAL MANIPULATION OF UTERINE ACTIVITY

Ritodrine

…

The effect of ritodrine in clinical practice is variable, possibly due to the multiple underlying pathophysiological processes. …

…

… it is therefore currently recommended (Royal College of Obstetricians and Gynaecologists 1994)[81] that ritodrine should be administered to delay delivery in order to implement measures which may improve fetal health, such as to:

(1) Promote fetal lung maturity by administration of steroids;

(2) Enable *in utero* transfer to a centre with appropriate neonatal facilities; or

(3) Delay delivery at a gestation which is normally associated with a very poor fetal outcome.

The administration of ritodrine for the treatment of preterm labour is associated with pulmonary, cardiac and pancreatic side effects (Clesham 1994). Many patients have mild symptoms of palpitations, anxiety, sweating, tremor or chest discomfort which limit the administration dose. The more serious side effects are pulmonary oedema, myocardial ischaemia, cardiac arrhythmia, hypotension and hyperglycaemia. There appears to be little difference in efficacy and side effects of ritodrine compared to other *β-sympathomimetics.*

…

Nifedipine

…

… there is good *in vitro* evidence that human myometrial, contractility is reduced by the dihydropyridines … The in vivo

[81] This appears to be inaccurate. Perhaps Professor Thornton had not read the endorsement to the Report – see main judgment.

evidence also supports a tocolytic effect. … In clinical studies (Keirse 1994c) the use of nifedipine was associated with fewer deliveries of babies less than 2500g and an increase in admissions to the neonatal intensive care unit.

…

Although some degree of myometrial relaxation has been demonstrated without major systemic side effects in the rat … in other species there are marked side effects. The most notable are due to l-type channel blockade in vascular smooth muscle. This causes vasodilatation with a fall in maternal blood pressure, increase in heart rate and reduction in uterine blood flow … In the primate, administration of nifedipine leads to a fall in fetal pO2 and pH with an increase in pCO2 … This is particularly worrying, since a similar effect in the human fetus would be likely to result in a deleterious effect on neonatal outcome. Nevertheless, clinical human studies have failed to demonstrate any effect of nifedipine on uterine blood flow in normotensive … or hypertensive … subjects, although an increase in admissions to the neonatal intensive care unit following maternal nifedipine … may be relevant.

…

Potassium channel openers

Repolarisation of the myometrial membrane is associated with the efflux of potassium through specific channels …

There are, as yet, no clinical trials which report the effect of potassium channel opening drugs administered to women in preterm labour. Evidence from *in vitro* experiments on human myometrium … support the use of these drugs as effective tocolytics and *in vivo* animal data suggests that spontaneous uterine activity is reduced by administration of potassium channel openers …

SUMMARY

The diversity of pharmacological agents which are currently promoted for the treatment of preterm labour testify to our lack of understanding of the basic process. Progress can only be made if the physiological and pathophysiological processes in the human are elucidated further. This area, with a few notable exceptions, has largely been neglected.

At present, only the *β-sympathomimetic ritodrine is licensed for the treatment of preterm labour. Administration is not without maternal risk and may not improve neonatal outcome.*

Nevertheless, it is an effective tocolytic since it causes a delay in delivery…

The … calcium channel blockers may be associated with adverse fetal effects and are not recommended for clinical use at present. However, in the rush to develop new tocolytics, it is important that we do not abandon existing drugs before the risks and benefits are fully determined…

In addition to the physiological and pathophysiological investigation of preterm labour, attention should be focused on obtaining useful information from clinical trials…

The judicious use of tocolysis is thus of paramount importance and these drugs must be administered in clinical practice with the same rigour that is required in research"