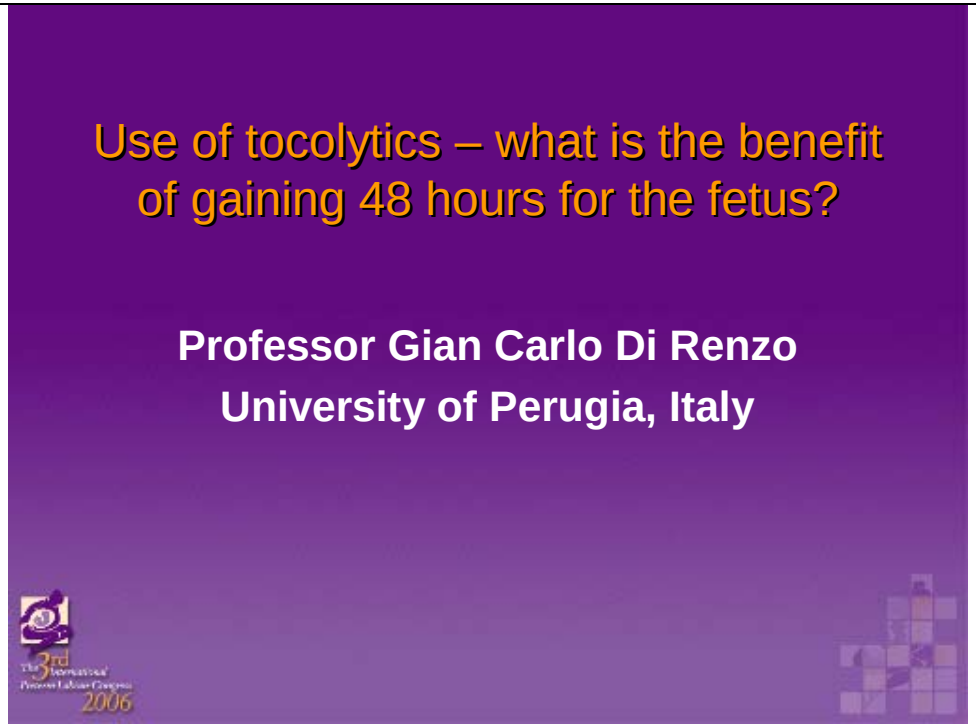
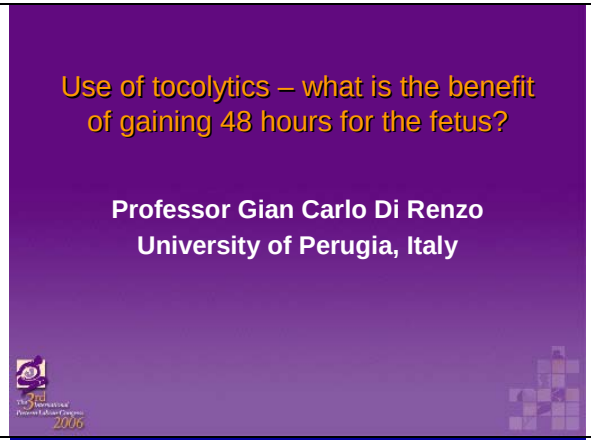


Presentation Details:
Slides: 51
Duration: 00:26:09

Slide 1

Use of tocolytics – what is the benefit of gaining 48 hours for the fetus?

Duration: 00:00:21
Advance mode: Auto



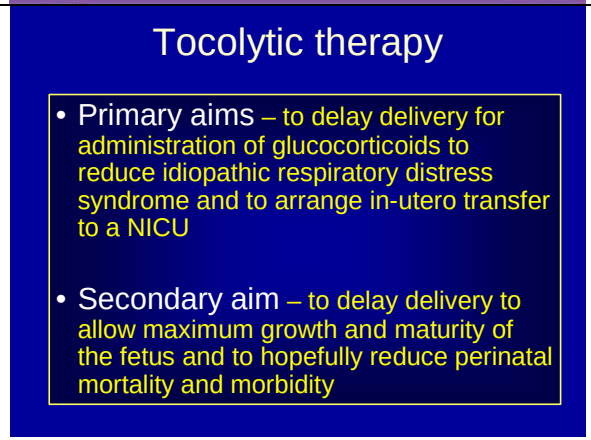
Notes:

Moderator: It is my pleasure to introduce Professor Gian Carlo Di Renzo, who will speak about the use of tocolytics. What is the benefit of gaining 48 hours for the fetus? You now very well Gian Carlo Di Renzo, who is the head of the Perinatal and Reproductive Center, at the University of Perugia.

Slide 2

Tocolytic therapy

Duration: 00:01:06
Advance mode: Auto



Notes:

Thank you Mr. Chairman, ladies and gentlemen, good afternoon. I think that in every text now, when we are dealing with the pre-term labour and the usual tocolytic therapy, we recognize that we have two aims. The first one, the primary aim, is to delay delivery for a short period of time in order to administer glucocorticoids; these are not only related to idiopathic respiratory distress syndrome, and to arrange in-utero transfer. We have compelling evidence that these two, and I will show you, that these two items have sound evidence that they are useful for very pre-term pregnancy.
The secondary aim is to delay delivery to allow the maturity of the fetus and to also reduce prenatal mortality morbidity. However, this second aim is not my task.

Slide 3

MYTHS TO DISPEL

Duration: 00:01:29

Advance mode: Auto

MYTHS TO DISPEL

- It may be worth pointing out that the incidence of SPB has not changed because we are now including more babies born at very early gestational age at extremely low birth weight at the limits of viability who were never included in our statistics in the past. There is also an increasing trend towards elective preterm delivery as neonatal intensive care has improved and finally that term delivery per se is not a good indicator of outcome bearing in mind that each day of delay between 22 and 28 weeks gestation increases survival by 3% without the need to get to full term

Notes:

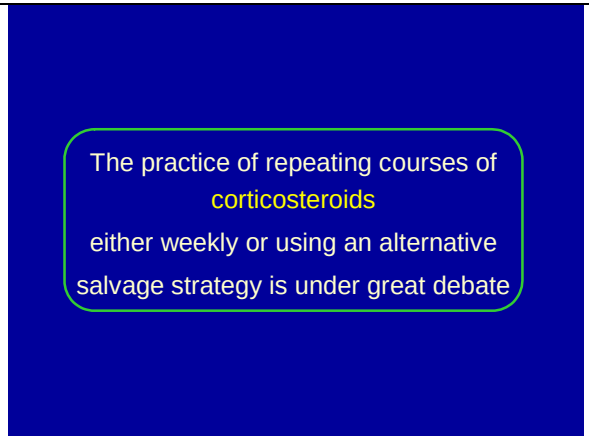
What are the first things I want to tell you? I was taking advantage of a comment of Ronnie Lamont in the guidelines we are setting up for the European Society of Perinatal Medicine, because I think that it is much better to try to take out some myths from our current practice. Before I make mine, and I would like to modify his point of view but I agree perfectly, that it is worth pointing out the incidence of spontaneous pre-term birth has not changed because we are now including more babies born at very early gestational age; we heard also Philip Steer yesterday about this, and who were never included in our statistical past.

There is also increasing trend towards elective pre-term delivery, of course the so-called electrogenic pre-terms as neonatal intensive care has improved. And finally, it has to be pointed out that term delivery per se is not a good indicator of outcome. Bear in mind that each day of delay the women reaches from 22 to 28 weeks gestation, increases survival by 3 percent without the need to get to full term. So, comparison may be worthwhile to be done within the limited subdivision of pre-term babies.

Slide 4 **MYTHS TO DISPEL** Duration: 00:00:38 Advance mode: Auto	MYTHS TO DISPEL • The myth that tocolytics only work for 48 hours arose because in the meta-analysis of beta-agonists it was found that 48 hours was the only consistent finding among the 16 papers analysed to allow comparison, but many tocolytics have been shown to work beyond 48 hours. It is just that it has become carved in stone as a result of that meta-analysis.	**Notes:** The second myth to be dispelled is that tocolysis should work at least, or, only for 48 hours. This was raised because of a meta-analysis on ß-agonist was done a few years ago, which found that the 48 hours was the only consistent finding among the 16 papers analyzed to allow comparison. But, as you know, many tocolytics are being shown to work beyond 48 hours. It is just a matter that it has become carved in stone as a result of that meta-analysis that we should compare tocolysis by 48 hours.
Slide 5 **MYTHS TO DISPEL** Duration: 00:00:25 Advance mode: Auto	MYTHS TO DISPEL • With respect to the claim no tocolytic has been shown to reduce the incidence of perinatal mortality and morbidity, it should be noticed that no tocolytic study has ever been carried out which has been empowered of a sufficient sample size to show such benefit.	**Notes:** The third point is that with respect to the claim that no tocolytic has been shown to reduce the incidence of prenatal mortality and morbidity, it should be noted that no tocolytic study has ever been carried out, which has been empowered of a sufficient sample size to show such a benefit. The following is not very, useful to deal with this matter without having some study on the background.

Slide 6 **CORTICOSTEROID PROPHYLAXIS** Duration: 00:00:08 Advance mode: Auto	**CORTICOSTEROID PROPHYLAXIS**	**Notes:** Having said that I think that I will concentrate my presentation mainly on the problems related to corticosteroid, why?
Slide 7 **Antepartum management** Duration: 00:00:48 Advance mode: Auto	**Antepartum management** Corticosteroids are most effective between 28 and 34 weeks' gestation; however, the published meta-analysis shows a beneficial but less significant effect at earlier gestational ages. Even though corticosteroid therapy does not completely decrease the incidence of RDS in infants born at 24 to 28 weeks' gestation, it does reduce the severity of RDS and the incidence of intraventricular hemorrage (IVH).	**Notes:** Because although everybody now agrees that, I say meta-analysis, Cochrane Review, whatever you want, systematic review, that corticosteroids are very effective, particularly between 28 and 34 weeks of gestation. But, there is also beneficial but less significant effect at earlier gestational ages, which is going down to 24 weeks. And, although it does not completely decrease the incidence of RDS, it does reduce in these particular ages, which we are much worried about, the incidence of intraventricular hemorrhage, and also, the severity of RDS, which is particularly important for the subsequent management after birth.

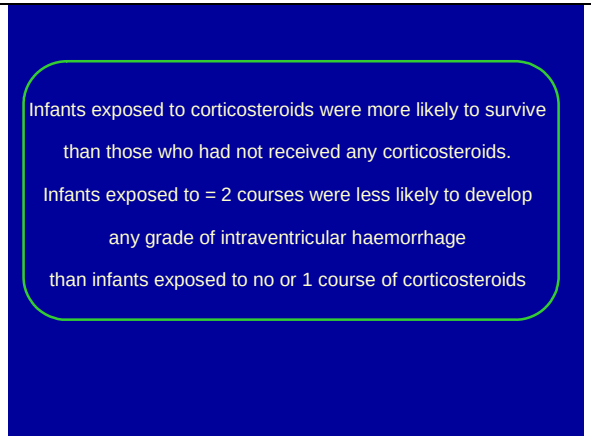
Slide 8 **CORTICOSTEROID PROPHYLAXIS** Duration: 00:00:31 Advance mode: Auto	**CORTICOSTEROID PROPHYLAXIS** • Betamethasone and dexamethasone are the two most widely used GC for antenatal prophylaxis, but there are no randomized controlled studies comparing these agents with respect to efficacy. Even though betamethasone seems to affect fetal heart rate variation and fetal movements more than dexamethasone, it seems to offer several advantages.	**Notes:** We agree that between the two most widely used glucocorticoids, betamethasone and dexamethasone, although there is no randomized trial comparing these agents in respect to efficacy, betamethasone seems to have major activities, especially on prevention of IVH. However, you know that compared to dexamethasone it has major effect of fetal heart rate variation and fetal movements.
Slide 9 **CORTICOSTEROID PROPHYLAXIS** Duration: 00:00:53 Advance mode: Auto	**CORTICOSTEROID PROPHYLAXIS** • It should be pointed out that the fetal biophysical variables recorded by CTG or ultrasound may be significantly modified by the corticosteroid administration, particularly betamethasone, and mothers should be informed or reduction of fetal movements in the 48 hours subsequent to drug injection. In the case of impending SPTL, betamethasone was administered in 12 mg, 12 hours apart, showing the same beneficial effects.	**Notes:** This is particularly important because since fetal biophysical variables recorded either by CTG or ultrasound may be significantly modified by the corticosteroid administration, and as I said, particularly by betamethasone. Mothers should be informed of the reduction of fetal movements in the 48 hours subsequent to drug injection. In the case of spontaneous pre-term labour it has been shown also that if we give just one course of betamethasone, 12 mg, but 12 hours apart instead of 24 hours apart, which is usually indicated, we may have the same beneficial effect. These more or less are the facts that everybody knows about corticosteroid prophylaxis, and these should be agreed by

		everybody.
Slide 10 **The practice of repeating courses of corticosteroids either weekly or using an alternative salvage strategy is under great debate** Duration: 00:00:45 Advance mode: Auto		**Notes:** However, there are points, which have been debated, particularly in the last years. First there was the practice of repeating courses of corticosteroids. These were being raised by two major factors. The first, with increasing multiple pregnancies many obstetricians started to treat these pregnancies as early as possible expecting a pre-term delivery in this pregnancy. The second is there being particularly high risk mothers, either for previous pre-term labour, or for maternal disease, that corticosteroids were given weekly in case there was a high chance that the particular pregnancy could end pre-term.

Slide 11

Infants exposed to corticosteroids were more likely to survive

Duration: 00:00:51
Advance mode: Auto



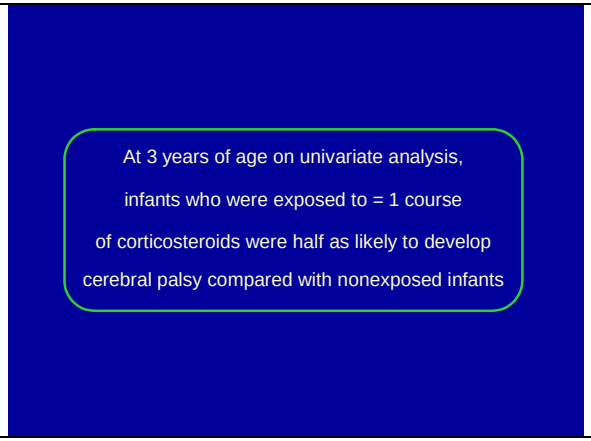
Notes:

What are the facts about repeated dosages of corticosteroids? You know there has been recently a result of a survey in Europe that has shown in some maternities some obstetricians use up to ten courses of corticosteroids in pregnancy. They start at 22 weeks and they go on until the unsafety is overcome so 34 weeks, which is too much. But mostly the mean is accepting to give two or three courses of corticosteroids.
What are the positive facts? First, infants exposed to corticosteroids are more likely to survive. If they are exposed to more than two courses of corticosteroids are less likely to develop any grade of intraventricular hemorrhage.

Slide 12

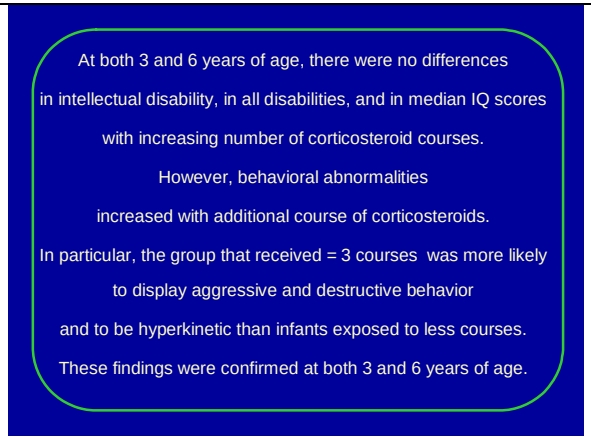
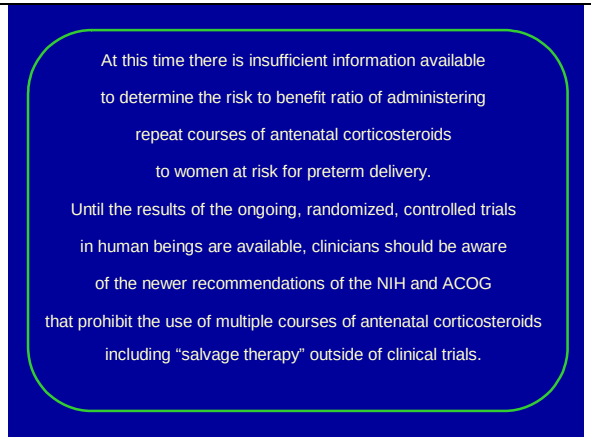
At 3 years of age on univariate analysis, infants who were exposed to = 1 course of corticosteroids...

Duration: 00:00:14
Advance mode: Auto



Notes:

The second is that at three years of age infants who received more corticosteroids are half as likely to develop cerebral palsy compared to non-exposed infants.

Slide 13 **At both 3 and 6 years of age, there were no differences ...** Duration: 00:00:41 Advance mode: Auto		**Notes:** Further, although there was no difference at three and six years of age in intellectual disability, or all disabilities, and IQ score with increasing number of corticosteroids courses, behavioral abnormalities start to appear. Those that received more than three courses of corticosteroids may display aggressive and destructive behavior, and be hyperkinetic compared to infants who received just one course. This finding has been confirmed in some studies just done recently.
Slide 14 **At this time there is insufficient information available...** Duration: 00:00:32 Advance mode: Auto		**Notes:** At this time however there is insufficient information to determine the risk to benefit ratio of administering repeated courses of antenatal corticosteroids. Until there are some ongoing studies, and they are available to clinicians, newer recommendations of the NIH and the American College of Gynecology still have a sort of prohibition to use multiple courses of antenatal corticosteroids, including salvage therapy outside of a clinical trial.

Slide 15

Comparison of pregancies delivering within and beyond 7 days of steroid administration – Neonatal outcomes

Duration: 00:00:39

Advance mode: Auto

Comparison of pregancies delivering within and beyond 7 days of steroid administration – Neonatal outcomes

	Delivery =7d (n=99)	Delivery >7d (n=98)	*p value*
Ventilation or CPAP >24 h (%)	63	81	<.01
Ventilation days*	0 (0-5)	1 (0-6)	.44
Surfactant use (%)	39	47	.28
Oxigen dependence at 28 d (%)	23	22	.92
IVH, any grade (%)	15	20	.33
IVH, grades 3 or 4	3	3	>.99
Sepsis (%)	19	22	.57
NEC, IVH; or sepsis (%)	31	28	.56

* Median (interquartile range).

Notes:

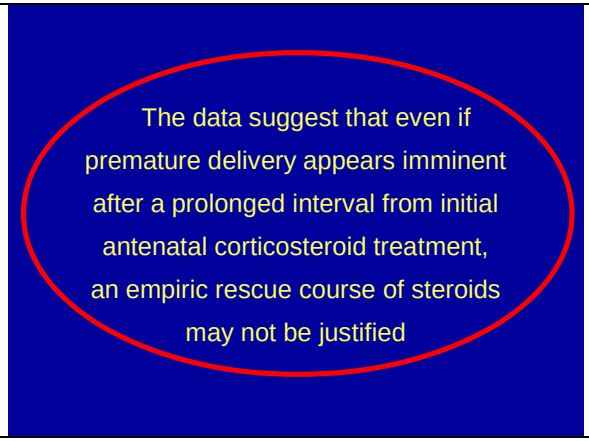
Another study, which has been particularly interesting and probably will come back in the discussion I will do after showing this clinical data, is that the (inaudible) after seven days the corticosteroids are not working any more, and you have to repeat. This was also one more reason why you repeat the courses. It has not been demonstrated in recent study, I was just presenting one of these showing that either if delivery was less than seven days after a full course of corticosteroids, or was more than seven days, the neonatal outcomes are the same.

Slide 16

The data suggest that even if premature delivery appears imminent after a prolonged interval...

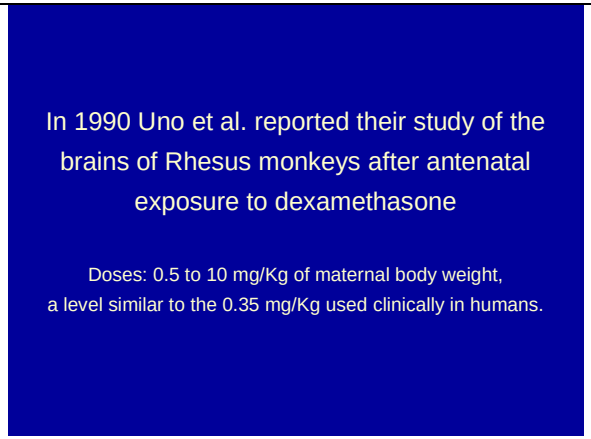
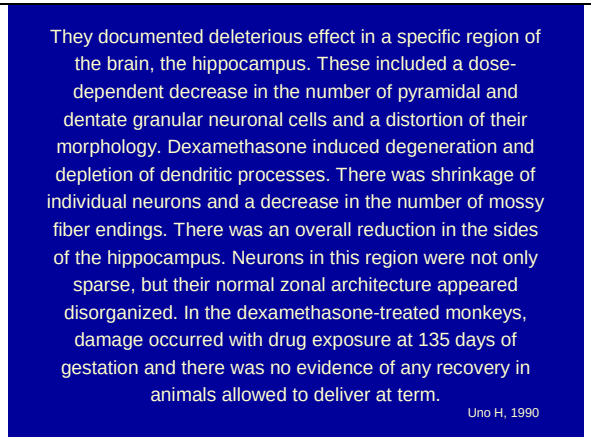
Duration: 00:00:13

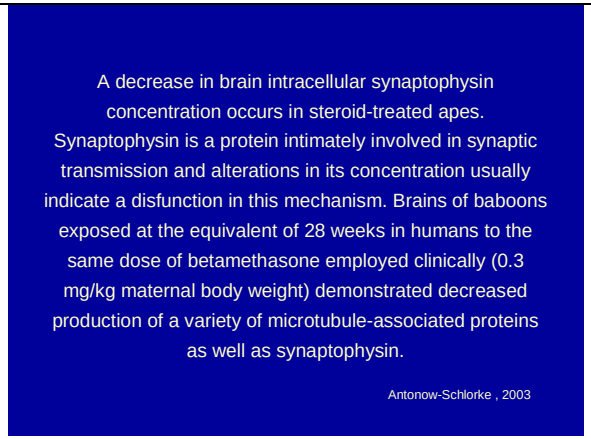
Advance mode: Auto

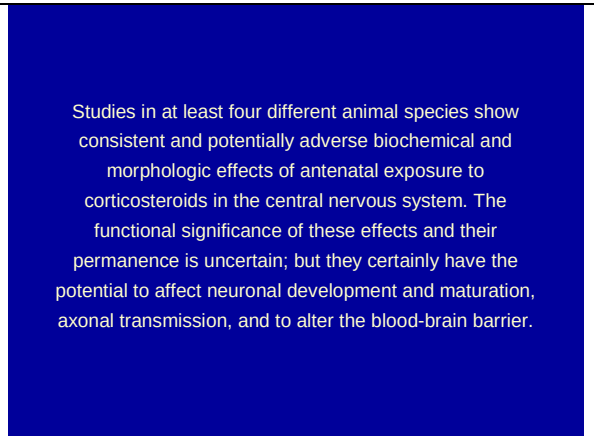
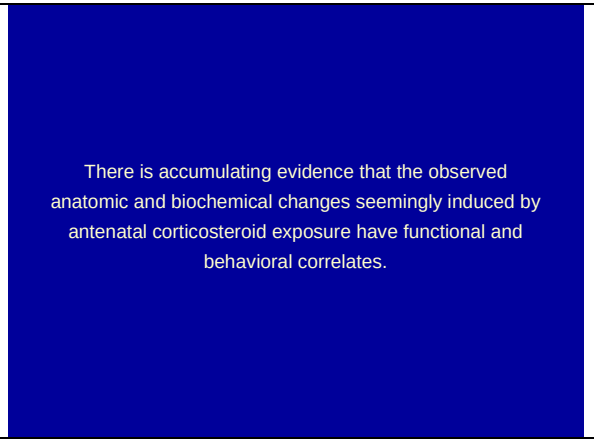


Notes:

So, this data suggests that even if premature delivery appears imminent after prolonged interval from initial antenatal corticosteroid treatment, an empiric rescue course of steroids may not be justified.

Slide 17 **In 1990 Uno et al. reported their study of the brains of Rhesus monkeys after antenatal exposure to dexamethasone** **Doses: 0.5 to 10 mg/Kg of maternal body weight, a level similar to the 0.35 mg/Kg used clinically in humans.** Duration: 00:00:35 Advance mode: Auto		**Notes:** Now, I want to discuss and show what are the counter-acting side effects of corticosteroids, which raise some worries about their use in the recent years. I think that not many of us have given too much attention to this particular study, which was produced more than 15 years ago. It was done in Rhesus monkeys, studying the brains after antenatal exposure of dexamethasone, a similar dosage to the one we use clinically in humans.
Slide 18 **They documented deleterious effect in a specific region of the brain, the hippocampus. These included a dose-dependent decrease in the number of pyramidal and dentate granular neuronal cells and a distortion of their morphology. Dexamethasone induced degeneration and depletion of dendritic processes. There was shrinkage of individual neurons and a decrease in the number of mossy fiber endings. There was an overall reduction in the sides of the hippocampus. Neurons in this region were not only sparse, but their normal zonal architecture appeared disorganized. In the dexamethasone-treated monkeys, damage occurred with drug exposure at 135 days of gestation and there was no evidence of any recovery in animals allowed to deliver at term.** Duration: 00:00:54 Advance mode: Auto		**Notes:** What this group of scientists showed was the deleterious effect in a specific region of the brain, called the hippocampus with a dose dependent decrease, that is particularly important in the number of pyramidal and dentate granular neuronal cells and distortion of morphology. Also the degeneration and depletion of dendritic processes, shrinkage of individual neurons and a decrease in the number of mossy fiber endings, and an overall reduction in the sides of the hippocampus. The neurons in this area not only appear sparse but their normal architecture appeared completely disorganized. This damage occurred at the

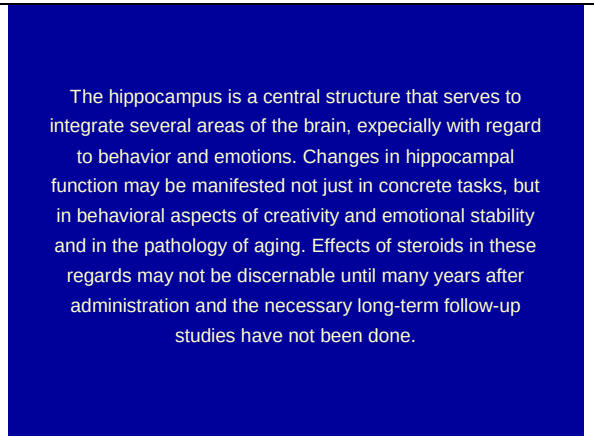
		gestational age of pre-term, and there was no evidence of any recovery afterwards.
Slide 19 **A decrease in brain intracellular synaptophysin concentration occurs in steroid-treated apes. Synaptophysin is a protein intimately involved in synaptic transmission and alterations in its concentration usually indicate a disfunction in this mechanism. Brains of baboons exposed at the equivalent of 28 weeks in humans to the same dose of betamethasone employed clinically (0.3 mg/kg maternal body weight) demonstrated decreased production of a variety of microtubule-associated proteins as well as synaptophysin.** Duration: 00:00:36 Advance mode: Auto		**Notes:** There was a decrease also of some particular protein like synaptophysin intracellular concentration occurred in the steroid treated apes. This protein is involved in the synaptic transmission, and alteration in its concentration indicates dysfunction in the mechanism in the brains of baboons exposed an equivalent of 28 weeks in humans, to the same dose of betamethasone. In this case another group later on, 12 years later, demonstrated decreased production of this particular protein.

Slide 20 **Studies in at least four different animal species show consistent and potentially adverse biochemical and morphologic effects of antenatal exposure to corticosteroids in the central nervous system. The functional significance of these effects and their permanence is uncertain; but they certainly have the potential to affect neuronal development and maturation, axonal transmission, and to alter the blood-brain barrier.** Duration: 00:00:34 Advance mode: Auto		**Notes:** There is now evidence in four different animal species that there are adverse biochemical and morphological effects of antenatal exposure to corticosteroids in the central nervous system. The functional significance of these effects, and their permanence, although it is uncertain they have potential, in any case, affect for neural development and maturation, axonal transmission, and the alteration in the blood-brain barrier.
Slide 21 **There is accumulating evidence that the observed anatomic and biochemical changes seemingly induced by antenatal corticosteroid exposure have functional and behavioral correlates.** Duration: 00:00:10 Advance mode: Auto		**Notes:** There is accumulating evidence that these anatomic and biochemical changes induced by antenatal corticosteroids have functional and behavior correlates.

Slide 22

The hippocampus is a central structure that serves to integrate several areas of the brain, expecially with regard to behavior and emotions. Changes in hippocampal function may be manifested not just in concrete tasks, but in behavioral aspects of creativity and emotional stability and in the pathology of aging. Effects of steroids in these regards may not be discernable until many years after administration and the necessary long-term follow-up studies have not been done.

Duration: 00:00:38
Advance mode: Auto



Notes:

Since the hippocampus is a central structure that integrates several areas of the brain, especially in regards behavior and emotion, this is in keeping with some of the results that I told you about repeated courses, and their clinical relevance at three and six years of age. However, the effect of steroids in these regards may not be discernible until many years after administration. The necessity for long term follow up studies have not been at least done properly, and are (in)conclusive.

Slide 23

Diagram illustrating the potential routes by which prenatal GC exposure leads to alterations in behavior and HPA activity in adulthood

Duration: 00:00:21
Advance mode: Auto

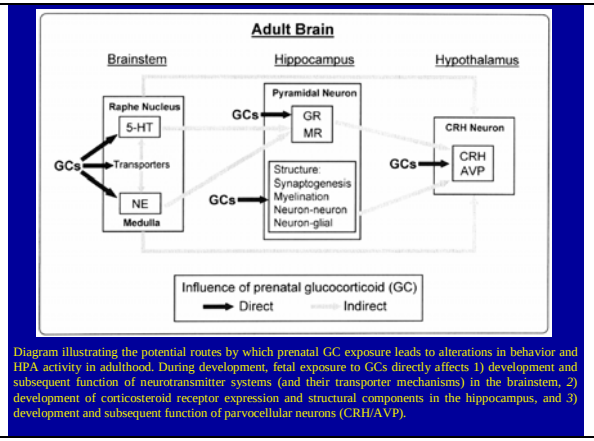


Diagram illustrating the potential routes by which prenatal GC exposure leads to alterations in behavior and HPA activity in adulthood. During development, fetal exposure to GCs directly affects 1) development and subsequent function of neurotransmitter systems (and their transporter mechanisms) in the brainstem, 2) development of corticosteroid receptor expression and structural components in the hippocampus, and 3) development and subsequent function of parvocellular neurons (CRH/AVP).

Notes:

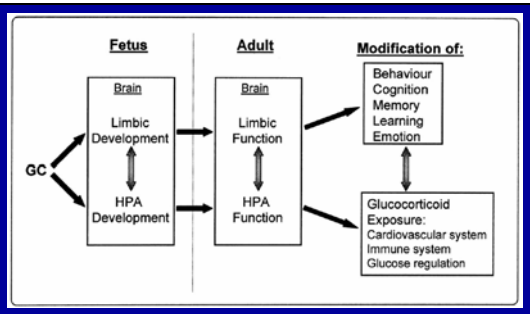
This schema shows how and in which structure glucocorticoids can affect the central nervous system, in the brainstem, especially in the hippocampus in which they may halt the synaptogenesis, myelination, neuron-neuron, neuron-glial interaction, and also at hypothalamic level.

Slide 24

Diagrammatic representation of the routes by which prenatal GC exposure programs adult behavior and neuroendocrine function

Duration: 00:00:42

Advance mode: Auto



Diagrammatic representation of the routes by which prenatal GC exposure programs adult behavior and neuroendocrine function. The fetal limbic system (primarily the hippocampus), hypothalamus, and anterior pituitary express high concentrations of corticosteroid receptors, and are sensitive to GCs. Exposure to exogenous GC at this time will alter development and subsequent function of both the limbic system and the HPA axis. The hippocampus regulates HPA function, and endogenous GCs (the end product of HPA activation) modify many aspects of limbic function. The *gray arrows* indicate this close functional association. In the periphery, the overall effect of programming during development will be altered exposure to endogenous GC throughout life. Increased exposure will predispose to a number of neurologic, metabolic, and cardiovascular diseases, whereas reduced exposure may act to protect against these diseases.

Notes:

In the fetus the limbic development and the development of hypothalamic pituitary adrenal axis is under the influence of glucocorticoids. This may bring later on, subsequently in life, especially after six years old, to modification of behavior, cognition, memory, learning and emotion. Also, there is now compelling evidence in animal studies, but some studies also of observation in humans, that exposure to glucocorticoids may alter the cardiovascular system, the immune system and the glucose regulation later on in life.

Slide 25

Several questions about ACS therapy require answers if we are to formulate rational clinical policies. Cerebral palsy commonly associated with preterm birth has a multifactorial etiology. Although some studies suggested that ACS therapy may be associated with a decrease in the incidence of cerebral palsy, this has not been a universal finding. In fact, if steroid therapy given to the neonate after delivery can cause decreased height, head circumference, motor skills and visual integration, in addition to lower IQ scores and cerebral palsy, could it be dangerous as well to give steroids immediately prior to delivery?

Duration: 00:00:50

Advance mode: Auto

Several questions about ACS therapy require answers if we are to formulate rational clinical policies. Cerebral palsy commonly associated with preterm birth has a multifactorial etiology. Although some studies suggested that ACS therapy may be associated with a decrease in the incidence of cerebral palsy, this has not been a universal finding. In fact, if steroid therapy given to the neonate after delivery can cause decreased height, head circumference, motor skills and visual integration, in addition to lower IQ scores and cerebral palsy, could it be dangerous as well to give steroids immediately prior to delivery?

Notes:

There are several questions about the use of glucocorticoids. One that is particularly interesting, and has been raised by neonatologists, is where obviously they were using glucocorticoids, for instance to prevent bronchial pulmonary dysplasia after birth. But what of yourselves thinking the case they used glucocorticoids for a long period to avoid bronchial pulmonary dysplasia increase the cerebral palsy. So, this is a strange connection between the fact that we have compelling evidence that glucocorticoids given before birth are protecting

		from cerebral palsy, while if you give after birth, they lower IQ score, they increase cerebral palsy and so they are considered very dangerous.
Slide 26 **RISKS OF ANTENATAL STEROIDS** Duration: 00:00:33 Advance mode: Auto	**RISKS OF ANTENATAL STEROIDS** • No changes in umbilical and uterine blood flows either in normal or IUGR fetuses • Vasodilatatory effects on placental bed in presence of high vascular resistance • Infants exposed to repeated courses have a significantly lower cortisol response to stressors than infants exposed to single course up to 7 days after birth	**Notes:** So, I think that these data, along with very recent data that shows infants exposed to repeat courses have also significantly lower cortisol response to stressor than infants exposed to single course up to seven days after birth. This can impair their facing (inaudible) later in life, although the effects of steroids have not been shown to make any variation to the umbilical or uterine blood flow; either you have normal, or intrauterine growth restricted, fetuses.
Slide 27 **Antenatal Steroid Therapy:** **Have We Undervalued the Risks?** Duration: 00:00:08 Advance mode: Auto	Antenatal Steroid Therapy: Have We Undervalued the Risks?	**Notes:** Should we put the question, have we really undervalued the risk of antenatal steroid therapy?

Slide 28

Given the risks, are there subgroups of patients that can be identified as most likely to benefit?

Duration: 00:00:14
Advance mode: Auto

Given the risks, are there subgroups of patients that can be identified as most likely to benefit?

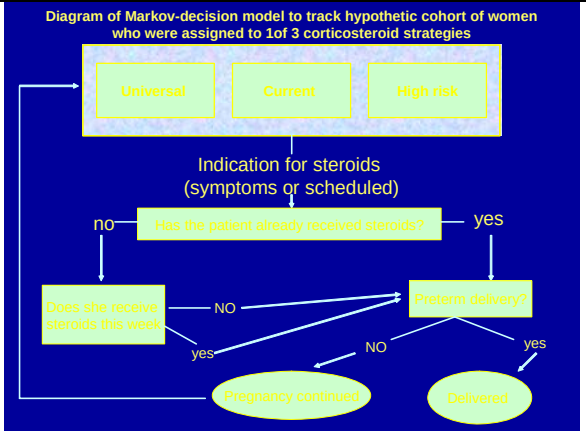
Notes:

Given the risk, are there any subgroups of patients that can be identified as most likely to benefit, so restricting the now universal way to give corticosteroid to any patient who is in treatment for pre-term labour?

Slide 29

Diagram of Markov-decision model to track hypothetic cohort of women who were assigned to 1of 3 corticosteroid strategies

Duration: 00:00:17
Advance mode: Auto



Notes:

This is a very interesting study, which has compared the possibility to use different strategies in giving corticosteroids universally to everyone, even though the pregnancy continues and the risk is not so high, to only high-risk populations.

Slide 30

The universal strategy would result in 249 fewer cases of RDS and 960,000 more women...

Duration: 00:00:26
Advance mode: Auto

The universal strategy would result in 249 fewer cases of RDS and 960,000 more women would receive corticosteroids per 1 million women (roughly 996 fewer RDS cases with 3,840,000 women receiving corticosteroids annually).

Notes:

The universal strategy has shown by some calculations that we may have 250 fewer cases of RDS, and if 960,000 per one million women would receive corticosteroids practically, we decrease by 1000 more or less RDS giving corticosteroids annually to four million women to avoid 1000 RDS cases.

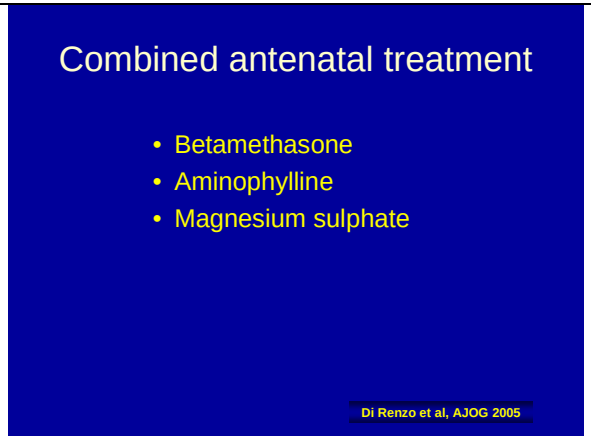
Slide 31 **The high-risk strategy would result in 35 fewer cases of RDS compared with the current strategy...** Duration: 00:00:37 Advance mode: Auto	The high-risk strategy would result in 35 fewer cases of RDS compared with the current strategy with 61,000 more women receiving corticosteroids per 1 million women (roughly 140 fewer RDS cases with 244,000 women receiving corticosteroids annually).	**Notes:** If we use the high-risk strategy, so population that is very high risk and we limit that, we will have 35 cases less of RDS compared to the current strategies, which is to give obviously with tocolysis and the usual, which I discussed at the beginning; we have 61,000 more women receiving corticosteroids per one million. This is roughly to say that if we limit to the high-risk strategy, we roughly have 140 less RDS', but we have to treat 250,000 women to receive corticosteroids annually.
Slide 32 **To prevent roughly 1000 RDS cases and 500 deaths, > 3 million women would be given corticosteroids annually under the universal strategy** Duration: 00:00:21 Advance mode: Auto	To prevent roughly 1000 RDS cases and 500 deaths, > 3 million women would be given corticosteroids annually under the universal strategy. Although the risks of the universal administration of corticosteroids are minimal, there are circumstances in which risk may outweigh benefit.	**Notes:** So, if we use the universal strategy to give corticosteroids to any woman who has threatened pre-term labour to avoid 1000 RDS cases, and possibly 500 deaths, we have to treat three million women. And although the risk appears minimal, there are circumstances in which the risk might outweigh the benefit.

Slide 33 **The practice of giving steroids to any mother with even a remote chance of delivery needs to be reexamined.** Duration: 00:00:20 Advance mode: Auto	The practice of giving steroids to any mother with even a remote chance of delivery needs to be reexamined.	**Notes:** So I think the practice of giving steroids to one mother with even remote chance of delivery needs clearly to be re-examined, because I show you that corticosteroids are not easy drugs as it appears, and may have long-term effects later on in adult life.
Slide 34 **Pre-term baby** Duration: 00:00:05 Advance mode: Auto		**Notes:**
Slide 35 **PREVENTION OF BRAIN DAMAGE** Duration: 00:00:19 Advance mode: Auto	PREVENTION OF BRAIN DAMAGE	**Notes:** In the next few minutes I want to show you that we may use much more properly the 48-hour gap that we need for the actual corticosteroid, and increase the possibility of preventing brain damage by adding some other drugs at the time we use just the course of corticosteroids.

Slide 36

Combined antenatal treatment

Duration: 00:00:31
Advance mode: Auto



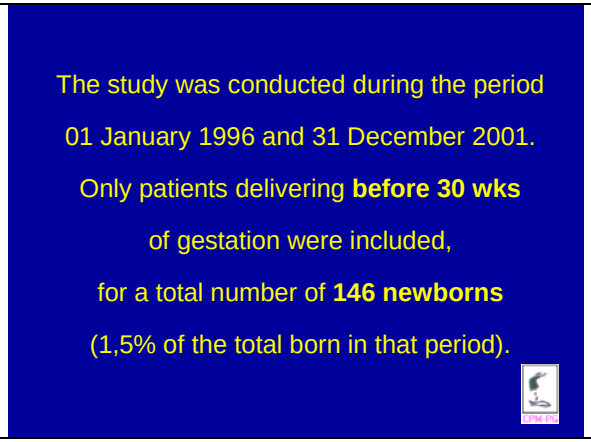
Notes:

This comes from a study that has been published last year in the American Journal. The study lasted six years in my department using combination treatment for 48 hours of obviously two courses of betamethasone along with aminophylline and magnesium sulfate. A low dosage given for 48 hours by intravenous route, 480 mg of aminophylline and 8.0 grams of magnesium sulfate a day, for two days, along with the betamethasone.

Slide 37

The study was conducted during the period 01 January 1996 and 31 December 2001. Only patients delivering before 30 wks of gestation were included, for a total number of 146 newborns (1,5% of the total born in that period).

Duration: 00:00:13
Advance mode: Auto



Notes:

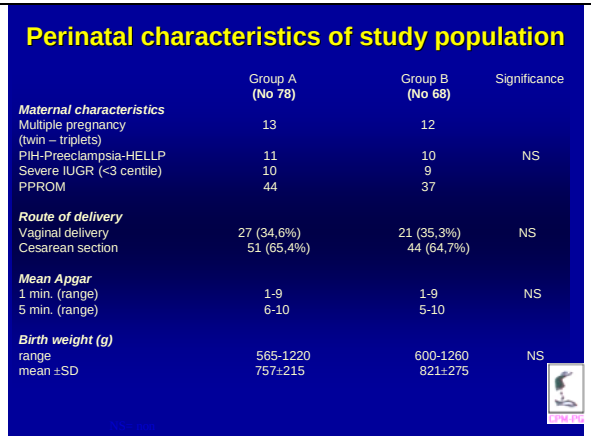
In this study, which ended in 2001, we only examined babies that were born before 30 weeks. In total we had in the two arms of the study, almost 150 newborns.

Slide 38

Perinatal characteristics of study population

Duration: 00:00:28

Advance mode: Auto



Notes:

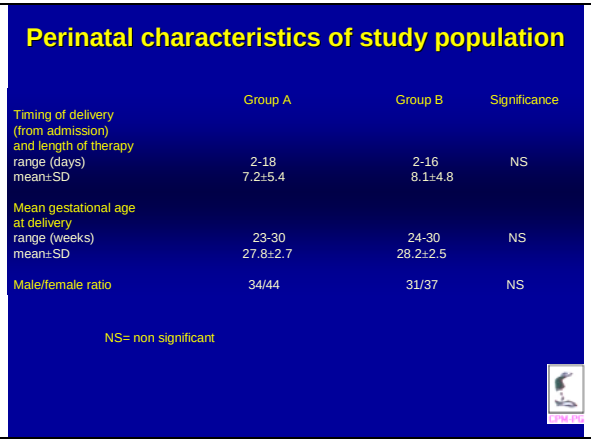
The two arms were those who were treated only by corticosteroids, and the other having corticosteroids plus these association. You can see that there is no significant difference between maternal characteristic in the group where we have 78 and the other 68. The birth weight of these babies were around 750 grams, and a little bit more in the group treated just with the corticosteroids, which is group B. Group A is the one with combination.

Slide 39

Perinatal characteristics of study population

Duration: 00:00:10

Advance mode: Auto



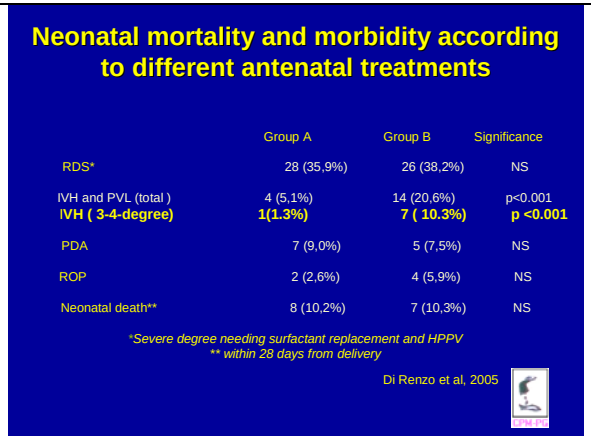
Notes:

There was no difference in male to female ratio, and mean gestational age of everybody was 27 weeks in the first group, and 28 and the second group.

Slide 40

Neonatal mortality and morbidity according to different antenatal treatments Group A Group B Significance RDS* 28 (35,9%) 26 (38,2%) NS IVH and PVL (total) 4 (5,1%) 14 (20,6%) p<0.001 IVH (3-4-degree) 1(1.3%) 7 (10.3%) p <0.001 PDA 7 (9,0%) 5 (7,5%) NS ROP 2 (2,6%) 4 (5,9%) NS Neonatal death 8 (10,2%) 7 (10,3%) NS*Severe degree needing surfactant replacement and HPPV** within 28 days from delivery**

Duration: 00:00:27
Advance mode: Auto



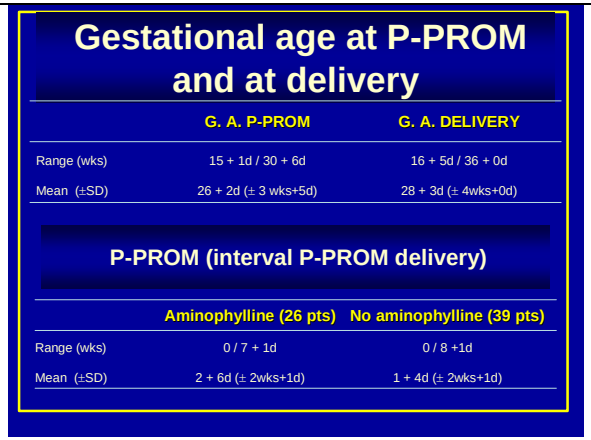
Notes:

What was the difference that we realized in the end? We expected really to observe less respiratory distress syndrome because aminophylline is an important respiratory drug, so we thought it could work a little bit more on respiratory distress. There was not much change in respiratory distress syndrome incidence, but we had a striking decrease of intraventricular hemorrhage of severe degree in the group treated by the combination drugs.

Slide 41

Gestational age at P-PROM and at delivery

Duration: 00:00:25
Advance mode: Auto



Notes:

Subsequently we have another observational study. The previous one was case control study but this is just observational. Using the same tool in pre-term P-PROM range around 26 weeks, they delivered two weeks later. We used the same 26 patients with aminophylline treated with this combination of drugs against the 39, which were not using this.

Slide 42

Aminophylline vs no aminophylline

Duration: 00:00:21

Advance mode: Auto

	Aminophylline (26)	No aminophylline (35)
Birthweight		
Range (grams)	470 – 2250	470 – 3080
Mean (±SD)	1273 (± 486.5)	1343 (± 524)
APGAR score I min.		
Range	1 – 9	0 - 9
Mean (±SD)	5 (± 2.5)	6 (± 2.7)
APGAR score 5 min.		
Range	2 - 9	2 - 10
Mean (±SD)	7 (± 2.1)	8 (± 2.2)
Days in NICU		
Range	1 – 135	1 – 120
Mean (±SD)	48 (± 42)	42 (± 32)

Notes:

You see that the mean birth weight of these babies is a little bit higher, also because we have an expectant management, so we leave the P-PROM to go over for some time. And the Apgar score is more or less similar, and also the days in neonatal intensive care are the same, and also the male to female ratio is the same.

Slide 43

Aminophylline vs no aminophylline

Duration: 00:00:42

Advance mode: Auto

	Aminophylline (26)	No aminophylline (35)
Death before 28 days	3 (11.5%)	2 (5.7%)
Intraven Hemorrhage (IVH 3-4)	**2 (7.7%)**	**8 (23%)****
Retinopathy (ROP)	3 (11.5%)	7 (20%)**
Patent ductus arter	2 (7.7%)	8 (22.9%)**
Respiratory distress (RDS)	16 (59,4%)	20 (57.1%)
Surfactant	15 (57.7%)	17 (48.6%)
Intubation	16 (59.4%)	17 (48.6%)
Anemia	6 (23%)	7 (20%)
Transfusions &/or Hepo	6 (23%)	7 (20%)
Hicterus	7 (26.9%)	16 (45.7%)**
phototherapy	7 (26.9%)	16 (45.7%)
Sepsis	2 (7.7%)	4 (11.4%)
Hypoglicemia	2 (7.7%)	1 (2.8%)
Other *	4 (15.4%)	7 (20%)
No complications	9 (34.8%)	12(32.1%)

* hyperglycemia, urin tract infections, etc.. ** p< 0.05

Notes:

The differences are not too much concerning the major, lets say complication with the neonates, but what is striking again is the very significant difference between intraventricular hemorrhage of a severe degree in the treated group, compared to the control, although we used the same management in the two groups. There is a limited observational study but I think that now there is some evidence that with very simple drugs, which have a very low cost, we may have for the 40,000 corticosteroids we may have something to avoid at least intraventricular hemorrhage in a consistent number of babies.

Slide 44

Key guidelines

Duration: 00:00:30

Advance mode: Auto

Key guidelines

- Administration of one single-course of antenatal glucocorticoids is the most important treatment to prevent brain injury and increase survival that can be provided by the obstetrician to patients at risk of preterm delivery at 24–34 weeks of gestation
- Based on observational clinical and animal studies, betamethasone is preferable to dexamethasone
- Multiple courses of corticosteroids should be avoided

Notes:

So what are the guidelines at the moment that are suggested? First, administration with single course of antenatal glucocorticoids is the most important treatment to prevent brain injury and increase survival that can be provided by the obstetrician to the patient at risk of pre-term delivery at 24 to 34 weeks of gestation. Based on observation of clinical and animal studies betamethasone is preferable to dexamethasone, but multiple courses of corticosteroids should be avoided.

Slide 45

TAKE HOME MESSAGES

Duration: 00:01:10

Advance mode: Auto

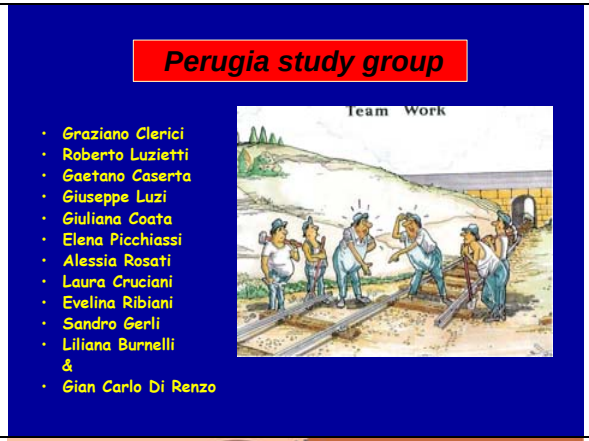
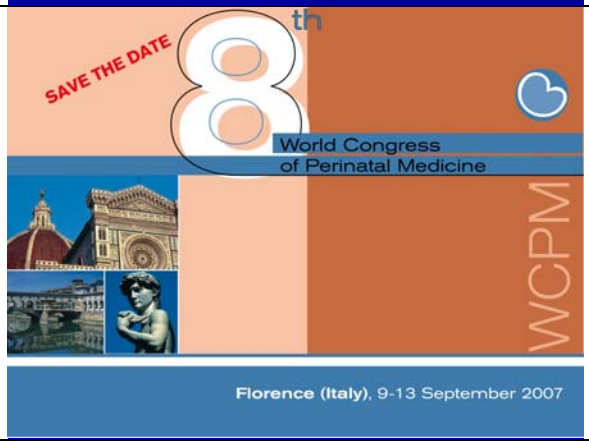
TAKE HOME MESSAGES

- Use safe tocolytics and for the shortest time
- Use steroids only once & when needed
- Use a combination of drugs (may decrease IVH)
- Use antibiotics (to prevent chorioamnionitis)

- **Consider that:**
  - **gaining 48 hrs at 24-33 wks is of benefit**
  - gaining 48 hrs at 34 weeks and beyond is of limited benefit

Notes:

Now, to answer the question, should we take advantage of 48 hours? Although I think that the 48 hours strict timing is a consequence of our attitude to try to make systematic our management in some particular occasion in pregnancy. I think that we may take advantage of 48 hours using safe tocolysis for the short time that is needed. Use the steroid only one time and only in a high-risk pregnancy patient. Maybe you will be convinced to use a combination of drugs, which may further decrease the intraventricular hemorrhage, along with betamethasone use. And obviously there is a

		question mark about using antibiotics if you are at risk of a chorioamnionitis particularly in preterm (inaudible0. So consider if we gain 48 hours this may be a benefit between 24 and 34 weeks. I do not think that after 33 weeks we may get any, or there is a very limited benefit to gain 48 hours in these pregnancies.
Slide 46 **Perugia study group** Duration: 00:00:06 Advance mode: Auto		**Notes:** I want to acknowledge my study group, which has been helping me all these years to make up some of the results that were presented.
Slide 47 **8th World Congress of Perinatal Medicine** Duration: 00:00:11 Advance mode: Auto		**Notes:** And I want to take this occasion also to invite you next year to the World Congress of Perinatal Medicine in Florence. I am one of the organizers for September 2007.

Slide 48

Thanks!

Duration: 00:00:02
Advance mode: Auto

Notes:

Thank you very much for your attention.

Slide 49

Q&A: Question

Duration: 00:00:20
Advance mode: Auto

Q&A

Question:

What were the reasons for the drop-out in the trial using aminophylline and magnesium sulphate?

Notes:

Question: There was a trial using aminophylline and magnesium sulfate, was this a placebo-controlled trial? And, I do not know, but I remembered the numbers that were entered in the study but I got the impression that there was a big drop-out. Can you give the reason for the drop-out rate?

Slide 50

Q&A: Response

Duration: 00:01:36
Advance mode: Auto

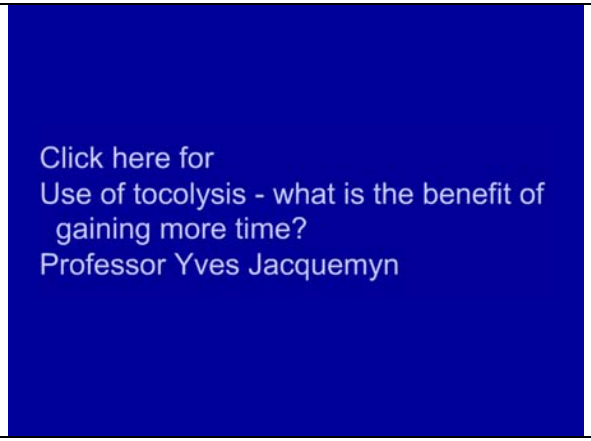
Q&A

Response:

What were the reasons for the drop-out in the trial using aminophylline and magnesium sulphate?

Notes:

Response: Oh yes, the Magpie Study you mean, the big study that was used for magnesium sulfate for utilization of tocolytic drugs. The first grams used by day were at least three times the one that I suggested in this study, so we are well aware that according to the dosage of magnesium sulfate, magnesium sulfate can be very dangerous for fetal brain. So there was a

		cut-off to probably not use more than 12 grams a day. This was also demonstrated by a recent study by the Croater group in Australia, which gave in one day magnesium sulfate in high-risk pregnancy delivered within 24 hours. They showed a decrease cerebral palsy and intraventricular hemorrhage in the treated group with magnesium sulfate, but no more than 12 grams compared to no treatment to placebo. I think that the usual magnesium sulfate at low dosages is being studied in animals by the group of Delivoria-Papadopoulos. They have convincing evidence that it is protective to the brain. If you use a higher dosage it is very dangerous. So I think this makes the difference between the result of one study and the result of other studies. We use, as I say, (no) more than eight grams a day, for two days.
Slide 51 **Next presentation** Duration: 00:00:05 Advance mode: By user Flash movie: text-direnzo.swf Display : In Articulate player		**Notes:**