

RITODRINE HCL FOR THE PREVENTION OF PREMATURE LABOR IN TWIN PREGNANCIES

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The perinatal mortality rate for twin gestation is in the range of 15%, and this is due predominantly to prematurity, although twins may also be born growth retarded. Ritodrine HCl, a beta sympathomimetic drug, has been shown to be effective, both in stopping premature labor and in preventing intrauterine growth retardation. With this in mind, a double-blind study using ritodrine HCl or placebo was begun in order to study its effect on premature labor, intrauterine growth retardation, and the perinatal mortality rate in twins. Thus far, 30 patients have delivered and have been followed to 6 weeks postpartum. Although the results on individual patients have remained blinded to the investigators, an initial evaluation of the ritodrine and placebo groups have revealed no difference with respect to gestational age, birth weight, or perinatal mortality. These preliminary results are not significant. However, it appears that ritodrine HCl is a safe oral agent for the antepartum gravida and her fetus. The study will be continued until approximately 100 patients have been enrolled.

The perinatal mortality (PNM) rate for twin gestation is in the range of 15%, and this high rate is due predominantly to prematurity, although intrauterine fetal growth retardation, polyhydramnios, congenital malformations, preeclampsia, placenta previa, anemia, uterine dysfunction, abnormal presentation, and prolapsed cord, all contribute to it.

Early diagnosis may be beneficial in preventing some of the complications of pregnancy and improving the PNM rate, but this is difficult because about 50% of twins are undiagnosed at the time of labor. Twins may be suggested by excessive uterine size, and the main tool we have for determining uterine growth is McDonald measurement, performed by stretching a centimeter tape from the symphysis over the abdomen to the most superior portion of the uterine fundus. Between 22 and 34 weeks gestation, this measurement in centimeters should equal weeks gestation, and a discrepancy of 4 or more centimeters suggests twins.

Ultrasound can confirm the diagnosis of twins. Theoretically, ultrasound, using the A and B mode, can make the diagnosis of twins as early as five weeks gestation from the visualization of two gestational sacs. At about 13 to 14 weeks, two fetal skulls can be appreciated. Universal ultrasound examination of all pregnant patients would certainly be of benefit in diagnosing all twins. X-ray, especially after 28 weeks, is also helpful in making this diagnosis. Clearly, as the number of fetuses in utero increases, the reduction in mean birth weight becomes more and more striking. In singleton pregnancies, deceleration in growth appears at 36 weeks; the curve for twins begins to fall away at 30 weeks; for triplets and quads, at 27 and 26 weeks respectively. Most patients with multiple gestation are asked to stay in bed, although the literature to support the concept that bed rest is beneficial is, at best, confusing. Recently, there have been reports of the use of uterine relaxant drugs in the prevention of premature labor in multiple gestation.

The use of Ritodrine hydrochloride for the prevention of premature labor is well-established. Ritodrine is a beta-sympathomimetic agent, an adrenalin-like drug. It acts on the beta receptors of the

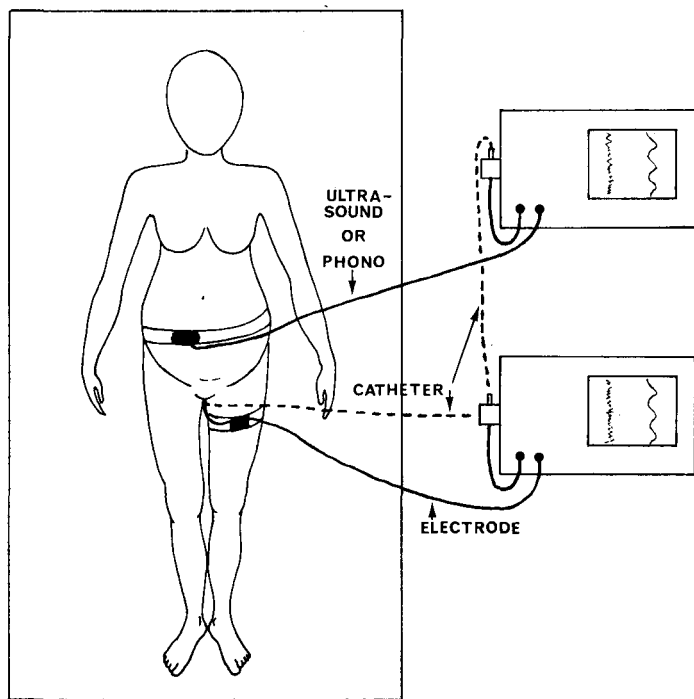


Fig. 1. A fluid-filled polyethylene catheter is passing transcervically into the uterine cavity, and this records intrauterine pressure shown on the lower fetal monitor. A catheter is then run between the strain gauge of the lower machine to the strain gauge of the upper machine and records uterine activity simultaneously on the second monitor. An electrode is attached to the presenting part of the first twin, and this records the instantaneous fetal heart rate on the lower machine. The heart rate of the second twin is picked up with an ultrasound Doppler or with the phonocardiogram, and this is shown displayed on the upper machine.

myometrium to decrease uterine activity. Generally, Ritodrine, as used for premature labor, is administered by intravenous infusion pump until contractions are diminished or abolished, and then the patient is begun on intramuscular Ritodrine, followed by an oral dose.

In a collaborative study carried out in Europe, Wesselius-de Casparis et al. (1971) reported a significant delay of premature labor in 80% of patients receiving Ritodrine, contrasted to 48% of those given placebo. In a study done at the University of Southern California (Nochimson et al. 1974), Ritodrine was shown to decrease uterine activity with minimal effects on the cardiovascular system. Following drug infusion, uterine activity decreased significantly from the control level, especially during the first ten minutes. Uterine activity is here expressed in uterine activity units. The major side effects were maternal tachycardia and a widening of the pulse pressure, largely a result of a drop in the diastolic pressure since the systolic pressure only increased minimally.

A number of authors have referred to the possible use of beta-sympathomimetic agents; in particular, Ritodrine hydrochloride for the treatment of intrauterine growth retardation, here defined as below the 10th percentile as defined by birth weights and gestational age. Early in the development of this drug, studies in animals to assess the effect on the offspring of prolonged administration to the mother in high doses showed no adverse effects. Surprisingly, the mean pup weights in rats were found to be significantly increased in the Ritodrine group, and the effect was dose-related.

These initial serendipitous findings raised the possibility of a practical use for Ritodrine in intrauterine growth retardation, but it was first considered worthwhile to perform more animal studies in experimentally-induced intrauterine growth retardation. After consideration of a number of possible animal models, one was selected which is attributed to Garmesheva (1968). He reported that cooling of pregnant rats on day 4 of pregnancy resulted in significant growth retardation of the fetuses.

Morsink and de Wachter (1973) found that in their hands maximum effect on pup weight was obtained by cooling to 20° C for three hours on day 8 of pregnancy. Fifty to sixty percent of the offspring of

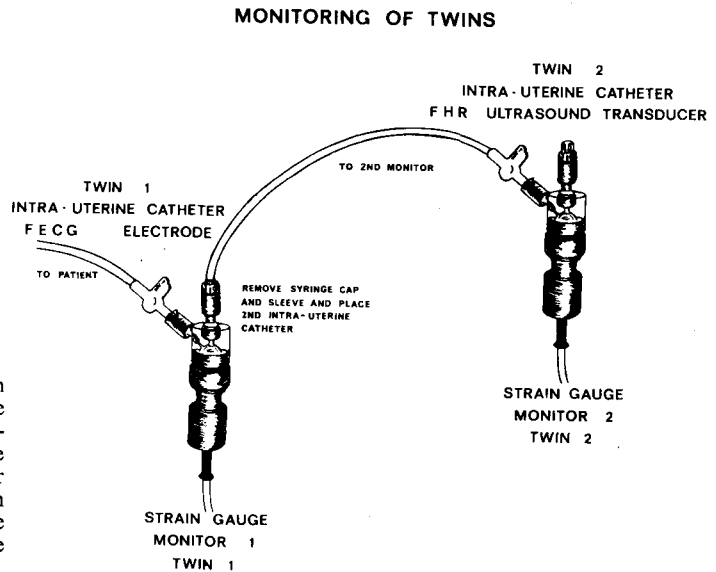


Fig. 2. The cap is removed from the second part of the strain gauge on monitor 1, and a second intrauterine catheter is placed here which goes to the second monitor and the second strain gauge. On the left-hand side, the intrauterine catheter is shown going to the patient.

the cooled rats were small for dates; that is, below the 10th percentile of the normal population. A series of further studies by the same investigators showed that the growth-inhibiting effect of cooling could be significantly counteracted by administration of Ritodrine from pregnancy day 7 to 20. Without Ritodrine, 61% of the offspring of cooled rats were growth-retarded, only 30% of the cooled rats which received Ritodrine. A comparison of the weight distribution of cooled rats and controlled rats, with or without Ritodrine administration, demonstrates that Ritodrine administration resulted in heavier pups, not by producing giant rats but by decreasing the incidence of the growth-retarded ones. A number of mechanisms were considered as being causal to the effect on infant weight. The effect of Ritodrine on glucose metabolism is shown here. Also, there have been suggestions that insulin is increased, and this may, therefore, cause a secondary increase in growth hormone.

Uterine blood flow is inversely proportional to intrauterine pressure. Since Ritodrine decreases intrauterine pressure by decreasing uterine activity, theoretically uterine blood flow over a long period will be increased. Also, Ritodrine increases cardiac output and may increase blood flow to the uterine and/or placental beds. Since twins are born both prematurely and growth-retarded and theoretically Ritodrine has the potential to prevent both of these conditions, a double-blind trial, using Ritodrine hydrochloride in twin pregnancy, was begun in order to study its effect on premature labor, intrauterine fetal growth retardation, and the perinatal mortality rate in twins. As soon after 20 weeks as the diagnosis of twins was made, the patient was entered into the study after an initial screening and was given Ritodrine or placebo prophylactically. The patients were then followed closely in the antepartum period with 24-hour urine estriol determinations, biparietal ultrasound measurements, and antepartum fetal heart rate and uterine contraction monitoring. Continuous fetal heart rate and uterine contraction monitoring was also done in the intrapartum period (Figs. 1 and 2). At birth, the infants were evaluated with Apgar scores, cord blood gases, and at 24 hours of age, a gestational age estimation, using the Dubowitz score. The infants are to be followed closely for five years with developmental tests.

Thus far, 30 patients have delivered and have been followed to six weeks postpartum. Although the results on individual patients have remained blinded to the investigators, an initial evaluation of the drug (Ritodrine) and the control (placebo) groups has revealed no difference with respect to gestational

age, birth weight, or perinatal mortality. These preliminary results are not significant. However, it appears that Ritodrine hydrochloride is a safe oral agent for the antepartum gravida and her fetus or fetuses. This study is being continued until approximately 100 patients have been enrolled. Recently, we had a very interesting patient deliver on this study who had conjoined twins, and I would like briefly just to present that case to you. We first saw this patient at approximately 35 weeks gestation when an X-ray of the abdomen revealed twins. Subsequently, an ultrasound examination was done and revealed a continuous thoracic cavity. This may represent the only ultrasonic in utero examination of conjoined twins. The twins were delivered by cesarean section and were found to be omphalo-xiphopagus. They expired soon after delivery, and an autopsy examination revealed an anomalous heart.

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