Family Practice Grand Rounds

Stillbirth

Douglas A. Bright, MD Chevenne, Wyoming

DR LOIS J. BECKER (*Chief Resident, University of Wyoming Family Practice Residency at Cheyenne*): Stillbirth is not an uncommon experience in family practice. Its event is attended by grief and difficult decisions that must be addressed by both the family and the delivering physician. Protocols have been established to assist the family physician when working with a family that is experiencing stillbirth. Presented here are a case of stillbirth and a discussion of management approaches.

J.B. was a 24-year-old woman who was first seen for prenatal care on March 20, 1989. She gave a history of having had a positive pregnancy test at a public health unit 4 weeks previously and a last normal menstrual period of January 16, 1989.

Her one previous gestation had been at age 17 years and had been complicated by ill-defined bleeding throughout the pregnancy. The child had been born approximately 4 weeks early and had been given up for adoption. The baby was male and weighed 4 pounds, 15 ounces.

The patient was healthy, and did not smoke or drink alcohol. Her past medical history was unremarkable. The uterus at that visit was approximately 8 to 9 weeks in size and her general physical examination was within normal limits.

She was followed throughout the pregnancy at frequent intervals, and beyond an early mild anemia (hemoglobin 120 g/L[12.0 g/dL]), no problems were apparent. Her total weight gain was 30 lb, uterine measurements followed dates, and blood pressure measurements and urine test findings were all normal.

On October 19, 1989, she arrived for her scheduled appointment at 37¹/₂ weeks' gestation. She had felt the baby move that morning, but not in the afternoon. No fetal heart sounds could be found with testing, and a

Submitted, revised, June 25, 1990.

From the University of Wyoming Family Practice Residency Program at Cheyenne. Requests for reprints should be addressed to Douglas A. Bright, MD, University of Wyoming Family Practice Residency Program at Cheyenne, 821 E 18th St, Cheyenne, WY 82001. quick-look level 1 ultrasound examination showed no fetal movement or heartbeat. She was in early, active labor.

The patient was admitted to the hospital. A confirmatory level 2 ultrasound examination verified the fetal death. The labor progressed rapidly. Membranes were ruptured artificially at 5:39 PM, she became completely dilated at 6:19 PM, was delivered of a stillborn male infant at 6:23 PM, and the placenta was expulsed at 6:25 PM. With the exception of thick meconium, the baby and placenta were normal to visual inspection. There was a midline episiotomy and repair. Estimated blood loss was 500 mL.

The patient was discharged the following morning. She has been followed up regularly, and is apparently doing well.

Pathologic evaluation of the placenta showed meconium staining, minimal amnionitis, and one small infarct. The autopsy showed a mature term male infant with an intrauterine death of undetermined cause.

Multiple maternal laboratory tests were evaluated, including those for *Taxoplasma*, cytomegalovirus, herpes simplex 1 and 2, and rubella; other tests included a Kleihauer-Betke stain for fetal cells, activated partial thromboplastin time for the so-called lupus anticoagulant, fibrinogen levels, and fibrin-split products, all of which were unremarkable.

Management of Fetal Death

DR FRED B. GAUPP (Assistant Professor, University of Wyoming Family Practice Residency Program at Cheyenne): The obstetric management of fetal death in utero has been simplified by recent developments. In the not too distant past, the diagnosis was mainly dependent on the inability to hear fetal heart tones. The definitive radiographic signs of fetal death, significant overlap of the skull bones and exaggeration of the curvature of the fetal spine, were either late events or inconsistently seen.

The diagnosis is now made quickly using real-time

© 1991 Appleton & Lange

The Journal of Family Practice, Vol. 32, No. 3, 1991

ultrasound, with lack of observed fetal motion on examination being definitive.¹ Once fetal death has been diagnosed, the question arises of how aggressive one should be in management.

Historically, watchful waiting was advocated. In 1957, Tricomi and Kohl² analyzed the data from 165 cases of fetal death managed conservatively: "90% of the patients went into labor within 14 days; 93% were delivered by the 21st day, and only 7% retained the products of conception for more than three weeks." One woman underwent cesarean section, however, after retaining a dead fetus for 120 days. Tricomi and Kohl felt that there was no increase in postpartum hemorrhage from this method. Since their paper was published, it has been recognized that, indeed, a definite risk of coagulation difficulties occurs with the retention of a stillbirth. This coagulopathy follows a gradual, predictable course, with even laboratory evidence not appearing until 3 to 4 weeks after the event³ and clinical bleeding lagging even further.

More recent reviews have found that women will usually give birth on their own well before the coagulopathy develops (the percentages have changed somewhat with time):

At least 75% of women labor spontaneously within 2 weeks of fetal death, and most of the others will have delivered by the time another two weeks have elapsed. However, some variation in this time table exists with respect to the timing and the cause of fetal death. As a general rule, the interval between death and spontaneous labor varies inversely with the stage of gestation at which the fetus dies.³

Kellner et al⁴ looked at patient choices:

At the time fetal death was diagnosed, 69 mothers were not in labor or had no medical indication for delivery. There was, therefore, the choice of immediate induction or waiting. All patients were given an explanation of the risks and benefits of immediate induction versus awaiting spontaneous labor. Patients were assured that, if they initially chose to wait but then changed their mind, labor would be induced. Immediate induction was chosen by 32 (46.4%) mothers, and 37 (53.6%) chose to wait. Of the latter, 19 went into labor spontaneously 2 to 42 days after diagnosis, and in 18, labor was induced 2 to 19 days after diagnosis.

Active management is dependent on the duration of the pregnancy and the state of the cervix. A near-term pregnancy with a favorable cervix can be treated with oxytocin, either alone or in combination with prostaglandins. Gestations of less than 28 weeks can be terminated with 20-mg prostaglandin E_2 vaginal suppositories.⁵ Very early fetal death is treated by surgical evacuation.

After the diagnosis or delivery of a dead fetus, an investigation should be done. Even though it may prove fruitless, there are compelling reasons to do so. On an individual basis, the most important question to be answered is, "Is it recurrent?" and secondarily, "Was it preventable?"—especially if the parents desire other children in the future.

The extent of the workup is somewhat controversial. Meier et al⁶ found that "among 87 neonatal and early infant deaths studied, the autopsy provided a cause of death in 67 (77%) while the clinical review provided a cause of death in 57 (65%) cases." There is little argument that a thorough case review and an autopsy are of value.

Regarding karyotyping, Mueller et al,⁷ after a review of 124 stillbirths, stated: "Although it has been suggested that karyotyping should be done routinely in any stillbirth or neonatal death, we believe that careful postmortem evaluation of these cases can often establish definitive diagnoses for which karyotyping is unnecessary," and "karyotyping is indicated when there is a family history of abnormal children or an obstetric history of recurrent pregnancy loss."

In addition, cultures and viral studies looking for evidence of infection with the TORCH syndromes (toxoplasmosis, rubella, cytomegalovirus, and herpes simpler 1 and 2) have a high enough yield to be done routinely.⁸ Serologic studies are also done.

A Kleihauer-Betke stain (of maternal blood, looking for fetal cells) may be helpful in selected cases. Laube and Schauberger⁹ looked at 29 cases of fetal death in which the diagnosis was in doubt and found that "Kleihauer-Betke staining of maternal blood was positive in four cases of unexplained fetal deaths. In all four the extent of feto-maternal hemorrhage was massive, amounting to 150 ml or more."

Other recommended studies for occult cases are cultures for *Listeria monocytogenes* and screening for the so-called lupus anticoagulant with coagulation studies.^{3,10}

In our case, the workup outlined above was done and no apparent cause was found. Our patient was advised not to become pregnant until the workup was completed. As no cause was discovered, the baby was at term, and she had no other risk factors, genetic counseling was offered but not strongly encouraged.

Regarding future pregnancy outcomes, in 1985, Freeman et al¹¹ reported on 7052 patients in a collaborative project, of whom 337 had suffered a previous stillbirth. Freeman and colleagues concluded:

a history of a previous stillbirth does have an influence on contraction stress test results and outcome parameters, but it is primarily seen within a group of patients with hypertension, clinical intrauterine growth retardation, or both. Certainly, however, as an isolated diagnosis, history of previous stillbirth carries a significantly higher risk for a positive contraction stress test than does postdate pregnancy (3.7%

continued from page 246

versus 1.6%) (p < 0.05) and, therefore, would continue to be an indication for antepartum fetal heart rate testing.

Supporting the Family

DR DOUGLAS A. BRIGHT (Assistant Professor, Family Practice Residency Program at Cheyenne): Loss of any type is difficult, but stillbirth is devastating. It is sudden and unexpected, and often occurs in a previously uncomplicated pregnancy. Stillbirth is also a true family tragedy. During the pregnancy, the mother and father, the siblings, and even the grandparents develop relationships with the baby. They fantasize about what it will be like, and have good and bad dreams about it.12

The grief and mourning accompanying a stillbirth follow a pattern similar to that seen in a death of any close family member, with predictable stages. After disbelief comes anger, and then disorientation.¹³ Stillbirth is unique, however, in that "although there is a sense of loss, there is little sense of having lost somebody."14

In fetal death there are two methods used to help with the mourning process. First, the birth and death of the baby is made more concrete by a variety of methods in the hospital. Second, bereavement counseling is employed both during and after the hospitalization.¹⁵

Is counseling necessary or even helpful? Pathological

grief has been reported to occur in up to one third of mothers who suffer a perinatal death.¹³ Intervention by grief support teams has been found to reduce the woman's anger and hostility, and to decrease physical symptoms. It is particularly effective for women who perceive themselves as having low levels of social support.¹⁶

Many hospitals have developed protocols to handle stillbirths (Appendix 1) and checklists (Appendix 2) that allow the staff to address the predictable difficulties in a consistent fashion. "In order to begin the grief process of a stillborn baby, the parents must face the reality of the loss. It is helpful for them to see and touch the baby, to name and describe it, to have a picture of it and to talk about it."12

The parents are allowed or encouraged to hold their baby. Tangible items are given to them-footprints, pictures, lockets of hair, the receiving blanket. All these are to make the child more real, both now and in the future.

Kellner et al4 found that nine out of ten parents chose to see their baby; in about one half of the cases a parent held the baby (54%); and the longer the gestation, the more often there was a funeral or memorial.

Whether the patient recovers in the postpartum area or on a medical-surgical unit varies with the institution and apparently has little or no long-range impact.¹⁷ On an individual basis the nursing unit can be quite signifi-



The diuretic that doesn't compromise cholesterol

BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure. Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide derived drugs

WARNINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals PHECADITIONS: Perform serum electronyte determinations at appropriate intervas, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance such as hyponatremia, hypochtomic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitals, such as increased vertincular irritability. Diutional hyponatremia may occur in edematous patients, appropriate treatment is useful useful to the total distribution of the sensitive of the sensiti

Unitional hypothaterithia may occur in event actions parents, oppromate reactions, to usually water restriction. In actual as id deplotion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances [liver, renal disease]. Hyperuricemia any occur, and frank gout may be precipitated in certain patients receiving indepande. Serum concentrations of unic acid should be monitored

periodically Use with caution in patients with severe renal disease; consider withholding of

use with caution in patients with severe retrai usease; consider withinoiding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically. Use with caution in patients with impaired hepatic function or progressive liver disease

Use wint cautor in parents with imparts include the cautor in projects the concept since minor alterations of fluid and electrolyte balance may precipitate hepatic cornar. Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Service moconcentrations of glucose should be monitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide Serum concentrations of calcium increased only slightly with indepamide in long-term studies of hypertensive patients. Indepamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.

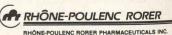
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepineptinine, but this does not preclude the use of norepineptinine. In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with 25% cumulative incidence. headche, dizziness, fatigue, weakness of the extremities, nervousness, tension, anxiety, intrability or agilation < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, adversion submitted and the statement of the statement o cumulative incidence: lightheadedness, drowiness, vertigo, insomnia, depression, biurred vision, constipaton, nauesa, vomiting, diarritane, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, papitations, frequency of urination, nocturia, polyuria, rash, hives, prurtus, vascultis, impotence or reduced litido, rhinorrhea, llushing, hyperuncemia, hyperglycemia, hypochloremia, hypochloremia, increase in serum BUN or creatinine, glycosura, weight loss, dry mouth, lingling of extremibles. Clinical hypotalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Uther adverse reactions reported with antihypertensive diuretics are intrahepatic cholestatic jaundice, siadentis, xanthogis, photosensitivity, uprurar, are nortorizing andiis, lever, respiratory reactions reported with antitype retrieval of the constrained and include a planned, sialadentis, xanthopsia, photosensitivity, purpura, necrotizing anglitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia. CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep tightly closed. Store at noom temperature. Avoid excessive heat. Dispense in tight containers as defined in USP. See product circular for full prescribing information. Revised: June 1990

References: 1. Horgan JH, O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response indapamide. Postgrad Med J 1991;57(Suppl 2);64-67. 2. Belling S, Vukwich RA, Ness Se, et al: Long-term experience with indapamide. *Am Near J* 1983;50(F); 17a1 (23& 262. 3. Weidmann P, Meier A, Mordasini R, et al: Diuretic treatment and setum lipoponteins: Effects of tienilic acid and indapamide. Klin Wochenschr 1981:59:343-346 4. Meyer-Sabellek W, Gotzen R, Heitz J, et al: Serum lipportein levels during long-ter treatment of hypertension with indapamide. *Hypertension* 1985;7(Suppl II):170-174. Scalabrino A, Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17-22. Plante GE, Dessurault DL: Hypertension in elderly patients: A comparative study between indapamide and hydrochlorothiazide. Am J Med 1988;84(Suppl 1B):98-103.



500 VIRGINIA DRIVE FORT WASHINGTON, PA 19034

© 1991 Rhône-Poulenc Rorer Pharmaceuticals Inc. LZ06291A 2/91 Printed in U.S.A. Product of Servier Research Institute

2(1)

FC#91-88-89

Stillbirth

continued from page 248

cant,¹⁸ and patient preference should be followed, if at all possible.

After hospitalization, follow-up is arranged with the physician and ideally with a local support group. Controversy exists over the value of lay groups, but "the importance of a social environment that recognizes the significance of the loss, validates the experience of grief, and accepts its expression should never be underestimated."¹⁹ Anecdotal data about the value of groups are abundant. As Cassem²⁰ has said, "Self-help groups continue to be among the most effective modalities for permitting expression of emotion, demonstrating that bereavement and its feelings are universal, and supplying the compassion and respect necessary for rebuilding self-esteem."

Dealing specifically with physician follow-up, Clyman et al²¹ found that 76% of the 108 families they studied chose to have this care postpartum. They commented that "certain features distinguished the parents who did not utilize the physician follow-up service: parents were less likely to utilize the service if they were not married, the mother was a teenager, the head of the household was unemployed, or there was no phone at home." Ironically, these groups would most benefit from these services.

Another aspect of the counseling that should be done is to gently prepare the grieving family for wellmeaning but clumsy efforts to comfort them. Remarks like "It's best it died before you got to know it,"¹⁴ or "You're young, you'll have more,"²² have been reported. Forrest et al¹⁵ even found a physician who asked a mother how she wanted her baby "disposed of."

The effects of a stillbirth on siblings have been examined.¹⁵ Particular difficulty was noted in children 3 and 4 years old. Statements such as "No one loves me in this house any more except my baby sister, and she's gone to live with Jesus," or "Why is Mummy sad? Is it the baby? What did I do wrong, hurt the baby, so it went away?" were reported. The children did well, however, with short grief reactions, except when their mothers' difficulties were prolonged.

How to deal with the other children in the family has been reviewed by Hardgrove and Warrick.²³ They pointed out that children do pick up the emotions and reactions of their parents, and that the tragedy needs to be discussed with them; that children cannot accept the explanation as a closed topic, that it will come up again and again. Children also need to know that mourning and sadness are appropriate and normal. A sensitive method of talking about the tragedy was suggested: "One way of explaining death is to help the child see the body as the house or package that life lives in rather than life itself. Parents do not need to explain everything. They can reply that they, too, wonder why some things happen."

Occasionally, the mother herself has contributed to the child's demise, through lack of prenatal care or use of cigarettes, alcohol, or drugs. At a time somewhat removed from the event her behavior must be addressed, especially if future pregnancies are planned. As the Assistant Secretary for Health has said,²⁴ "We must ensure that they understand their own responsibilities for the new life growing within them."

Wolff et al¹⁷ have done some interesting (and unsettling) work, especially in the area of who (if anyone) is to blame: "In dealing with their reasons for the loss of the baby, our data are too small to permit much interpretation. On the surface, half either blamed themselves or projected blame onto others; a quarter of them attributed the cause to God's will, which can be interpreted variously; and a quarter consciously or unconsciously avoided dealing with this loaded concept in any way."

Long-range follow-up is hopeful. "Of those followed, 50% became pregnant again. 80% of these pregnancies were planned immediately after the death of the baby."¹⁷ Even those who, for whatever reason, avoided future pregnancy, seemed to do well. "Of those who verbalized the intention not to become pregnant again, half did not in the three-year follow-up. These women did not become depressed or in other ways obviously psychologically restricted, indicating that for them, at least, pregnancy was not necessary to maintain their equilibrium."¹⁷

Physicians and other caregivers experience their own difficulties with stillbirth. They feel a guilt very similar to that the family experiences.²⁵ Unfortunately, caregivers may actually avoid the patient in order to protect themselves emotionally.¹⁴ Bourne²⁶ was struck by the effects stillbirths had on the physicians involved, which were more pronounced than those of the patients themselves. In surveys he found "a strong reluctance of doctors to know, notice or remember anything about the patient who has had a stillbirth." As a result, "It seems that, in addition to her own sadness and anxieties, a woman experiencing a stillbirth is liable to be bereft of medical help owing to the unconscious alienation of her doctor's interest from her and her family or because the doctorpatient relationship breaks down."

To combat emotional isolation, a team approach is commonly used. "No one physician or nurse can assume the entire burden of supporting the patient and her family. We recommend the creation of a perinatal be reavement team, whose members can share the tasks of helping the mother and her family. In addition they can help each other."¹⁴

continued on page 252

Stillbirth

Conclusions

"With this death comes the end of a dream."22

Those of us involved in the care of these families have multiple responsibilities. We must investigate for the cause, specifically looking for recurrent or preventable causes. We should strive not only to provide support for these people but also to make sure that they have the tangible items: the pictures, the hair, the blankets, to facilitate the mourning process. "The end point of the grieving process is not to forget the loved one but to remember without feeling so much pain."12

References

- 1. Hagen-Ansert SL. Textbook of diagnostic ultrasonography. 3rd ed. St Louis, Mo: CV Mosby, 1989:466.
- Tricomi V, Kohl SG. Fetal death in utero. Am J Obstet Gynecol 1957; 74:1092-7.
- Pitkin RM. Fetal death: diagnosis and management. Am J Obstet Gynecol 1978; 157:583-9
- 4. Kellner KR, Donnelly WH, Gould SD. Parental behavior after perinatal death: lack of predictive demographic and obstetric variables. Obstet Gynecol 1984; 63:809-14.
- 5. Diagnosis and management of fetal death (ACOG technical bulletin 98). Washington DC: American College of Obstetricians and Gynecologists, 1986.
- 6. Meier PR, Manchester DK, Shikes RH, et al. Perinatal autopsy: its clinical value. Obstet Gynecol 1986; 67:349-51.
- 7. Mueller RF, Sybert VP, Johnson J, et al. Evaluation of a protocol for postmortem examination of stillbirths. N Engl J Med 1983; 309:586-90.
- 8. Naeye RI. Causes of perinatal mortality in the US collaborative perinatal project. JAMA 1977; 238:228-9.
- Laube DW, Schauberger CW. Fetomaternal bleeding as a cause for "unexplained" fetal death. Obstet Gynecol 1982; 60:649-51.

- 10. Branch DW, Scott JR, Kochenour NK, Hershgold E. Obstetric complications associated with the lupus anticoagulant. N Engl Med 1985; 313:1322-6.
- 11. Freeman RK, Dorchester W, Anderson G, Garite TJ. The significance of a previous stillbirth. Am J Obstet Gynecol 1985; 151:7-13.
- 12. Lewis E. The management of stillbirth, coping with an unreality Lancet 1976; 2:619-20.
- 13. Lake M, Knuppel RA, Murphy J, Johnson TM. The role of a grief support team following stillbirth. Am J Obstet Gynecol 1983: 146:877-81.
- 14. Stack JM, Barnas K. Stillbirth. Am Fam Physician 1987; 35:117-24.
- 15. Forrest GC, Standish E, Baum JD. Support after perinatal death a study of support and counseling after perinatal death. Br Med I 1982; 285:1475-9.
- 16. Lake MF, Johnson TM, Murphy J, Knuppel RA. Evaluation of a perinatal grief support team. Am J Obstet Gynecol 1987; 157:1203-6.
- 17. Wolff JR, Nielson PE, Schiller P. The emotional reaction to a stillbirth. Am J Obstet Gynecol 1970; 108:73-7.
- 18. Oglethorpe RJL. Stillbirth: a personal experience. Br Med J 1983; 287:1197-8.
- 19. Condon JT. Management of established pathological grief reaction after stillbirth. Am J Psychiatry 1986; 143:978-92.
- 20. Cassem NH. Treating the person confronting death. In: Nicholi AM, ed. The Harvard guide to modern psychiatry. Cambridge, Mass: Harvard University Press, 1978:599.
- 21. Clyman RI, Green C, Mikkelsen C, et al. Do parents utilize physician follow-up after the death of their newborn? Pediatrics 1979; 65:665-7.
- 22. Taylor PB, Gideon MD. Crisis counseling following the death of a baby. J Reprod Med 1980; 24:208-11.
- 23. Hardgrove C, Warrick LH. How shall we tell the children? Am] Nurs 1974; 74:448-50.
- 24. Mason JO. From the assistant secretary for health. JAMA 1989. 262:2202
- 25. Bruhn DF, Bruhn P. Stillbirth, a humanistic response. J Reprod Med 1984; 29:107-12.
- 26. Bourne S. The psychological effects of stillbirth on women and their doctors. J R Coll Gen Pract 1968; 16:103-12.



The diuretic that doesn't compromise cholesterol

BRIFF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of Horocritical and conditions of the condition of the standard of the treatment of the treatment of salt and fluid retention associated with congestive heart failure. Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamidederived drugs

WARNINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hypotartemia, hypotheremic alkalosis, or hypotakelmia. The risk of hypotakelma secondary to diuresis and natriuresis is increased with larger doses, with brick duresis, with severe cirritosis, and with concommatint use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypotalemia. Hypotalemia can sensitize or exaggerate threagons of the heart to the toxic effects of digitalis, such as increased vertincular infrability. Diutional hyponatremia may occur in edematous patients; appropriate treatment is usally water restriction. In actual ad delection. according the restreent is the such water effective.

usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).

Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored

periodically Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should

baccommonly in progressive relian impaintent is busieved. An an uncludin tests should be performed periodically. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiad administration. Serum concentrations of glucose should be preshered using during the means with ideations.

be monitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed. Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

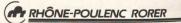
DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with $\geq 5\%$ cumulative incidence: headache, dizziness, fatigue, weakness, reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaies, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irratibility or aptiation, 55% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, biurred vision, constigation, naues, vontingi, diarrha, gastric irritation, addominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular haerb tael, taplatioations, frequency of unitation, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hypergycemia, hypochtoemia, hypochtoemia, increase in serum BUN or creatinnie, glycosuria, veight loss, dri y nouti, figling of extremities. Clinical hypotakiemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-tems tudy (157 patients) potasism uspotementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antityprentienvie/durients ex intrahepatic cholestatic jaundice, siadeentis, xanhopsia, photosensitivity, purpura, necrotizing anglits, fever, respiratory distress (including pneumonits), anaphylacite reactions, agranulocytosis, leukopena, thromoborytopena, aplastic aremia. thrombocytopenia, aplastic anemia

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription Keep tightly closed. Store at room temperature. Avoid excessive heat. Dispense in tight containers as defined in USP. See product circular for full prescribing information. Revised: June 1990

References: 1. Horgan JH, O'Donovan A, Teo KK: Echocardiographic evaluation of left Interesties: 1. Horgan JP, Obbitvari A, Ieo XA. Corocarologiapine evaluation of the untricular function in patients showing an antihyperanise and biochemical response indapamide. *Postgrad Med J* 1981;57(Suppl 2):64-67. 2. Beling S. Vukovich RA, Neis ES, et al. Long-term experience with indapamide. *Am Hear J* 1983;106(1, Part 2):85-622. 3. Weidman P. Meier A, Moradain R, et al. Diurecti treatment and serum lio-proteins: Effects of tienilic acid and indapamide. *Klin Wochenschr* 1981;59:343-34. proteins: Enters of telluit ado and indigamide. *Xini Wocherson* 1991;33:34-3-34 (A. Meyer-Sabeliev W. Gotzen, R. Hutz, J. et al. Serum (bioprotein levels during tong-tem treatment of hypertension with indigamide. *Hypertension* 1985;7(Suppl 2):170-174 5. Scalabrino A. Galeone F. Giuntoli F, et al. Clinical investigation on long-term effects of indigamide in patients with essential hypertension. *Curr Ther Res* 1984;57(S1):1722. 6. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiladia add before T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiladia add *Vecel* Merce. b. Potter I, Lithell H, Berne C: A comparison of the effects of hydrochloroflizide and captopil on pluces and lipid metabolism in patients with hydretrison. In *Ergl J Mid* 1998; 221(13):858-873. 7. Williams GH: Converting-enzyme inhibitors in the tratamet ism, calcium-channel blocking agents, and hypertension maragement. *Drag Intel Oin Pharm* 1986;22:659-671. 9. Von Funcke H, Von Bredow Ch, Cermakova E, Lodef (indpagnide) In the tratament of hypertension: Multicenter study in 3301 hypertensive. *Fortschr* Med 1986;104(6):133-139. 10. Data on file, Rhöne-Poulenc Rorer Pharmaceuticals Inc. Pharmaceuticals Inc.



RHÔNE-POULENC RORER PHARMACEUTICALS INC 500 VIRGINIA DRIVE FORT WASHINGTON, PA 19034

© 1991 Rhône-Poulenc Rorer Pharmaceuticals Inc. LZ06291A 2/91 Printed in U.S.A. Product of Servier Research Institute FC#91-88-89

5(L)