Dipyprone (Optalgin®) is a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase-1 and cyclooxygenase-2 activity, thereby reducing the production of prostaglandin E2 and E1. This effect is not unique to pregnant women or fetuses but occurs widely in adults, particularly in patients with contracted intravascular fluid volume as a result of congestive heart failure, cirrhosis, diuretic use, or restricted sodium intake. All these clinical situations are at increased risk for NSAID-related changes in renal function. The drug is widely used in many countries as an analgetic and antipyretic agent, especially in some parts of Europe, South America and Asia. It was banned in the United States by the Food and Drug Administration in 1977 because of a possible association with agranulocytosis. In contrast to other NSAIDs, precautions regarding the use of dipyprone during pregnancy are not well defined and information on its safety in pregnancy is scarce. A weak association with Wilms' tumor was found in children of women who took dipyprone during pregnancy [1]. Other suggested adverse effects are leukemia and neural tube defects found in mice. The association of NSAIDs with oligohydramnios was described in a series of patients who took indomethacin [2], and in only two case reports of dipyprone use. In this case, oligohydramnios and restricted ductus arteriosus was described in a healthy 21 year old woman [3]. Catalan et al. [3] reported a case of a term pregnant woman who suffered from renal colic treated with high dose dipyprone and who developed oligohydramnios 60 hours after treatment initiation. Thirty-five hours after dipyprone was discontinued the AFI returned to normal. In the second report, Sanchez-de-la-Nieta and colleagues [4] described a healthy 21 year old woman who developed maternal acute renal failure, rash and oligohydramnios (AFI 20 mm) 10 days after taking dipyprone, 1.5–3 g a day for 10 days, to relieve her back pain. Following treatment with intravenous fluids and dipyprone discontinuation the rash disappeared and blood analyses and the AFI returned to normal (AFI 60 mm).

Dipyprone associated with renal failure during pregnancy may be explained by two possible mechanisms: a) reversible renal ischemia secondary to inhibition of prostaglandin synthesis, and b) acute tubulointerstitial nephritis. Both cases, as well as ours, suggest a possible effect of the drug on fetal kidney function, reflected by the reduction in amniotic fluid index. The two previous case reports mention the use of high dose magnesium dipyprone, whereas in our patient the compound used was sodium dipyprone. Cases of agranulocytosis and aplastic anemia were reported with the sodium compound but we are not aware of differences in effect between magnesium and sodium on the ductus arteriosus or fetal kidneys.

In all cases described, including the present report, dipyprone withdrawal was associated with a dramatic improvement in the amniotic fluid volume. In these cases, the mechanism of oligohydramnios is probably related to the reduced produc-
Sodium dypirone can induce two different forms of acute renal failure: a) reversible renal ischemia secondary to inhibition of prostaglandin synthesis, appearing 3–7 days after initiation of therapy when drug levels inhibit prostaglandin synthesis; and b) acute tubulointerstitial nephritis. In our patient two fetal effects were seen: oligohydramnios and the constriction of the ductus arteriosus. In our patient as well as in the two patients previously reported, high doses of dipyrene were used by pregnant women. In one report, acute renal failure occurred in the mother together with oligohydramnios in the fetus [3]. In our case as in one other case report, maternal renal function was normal. The present report is the first to describe an effect on the ductus arteriosus. In all three case reports the withdrawal of dipyrene was associated with an increase of maternal renal function and reduced fetal effects. We suggest that dipyrene is a possible cause for both adverse side effects [5]. Prior studies have not evaluated the function of the ductus. Our case report suggests a close relationship between restriction of the ductus size and oligohydramnios and may shed light on the mechanism of the latter. In summary, prior case reports have shown an association between dipyrene use and oligohydramnios. In our case, oligohydramnios was also associated with restriction of the ductus arteriosus; both were reversible. Because of this possible association, we recommend that dipyrene be used with caution. Since all cases were induced by high doses of dipyrene, it is feasible that low dosage and limited length of usage should be practiced until further safety studies are performed. We recommend prescribing other analgesic drugs – for example, acetaminophen (Tylenol®, Acamol®, Paracetamol®) or morphine derivatives in cases of more severe pain – that have few long-term side effects on the fetus. In cases where inadvertent high dosages are used in the third trimester we recommend evaluation of the width of the ductus arteriosus, the amniotic fluid volume, maternal renal function, and complete blood counts.

References

Correspondence: Dr. D. Mankuta, Dept. of Obstetrics and Gynecology, Hebrew University Hospital, P.O. Box 12000, Jerusalem 91120, Israel. Phone: (972-2) 677-6484 Fax: (972-2) 579-1070 email: mankuta@yahoo.com

Capsule
Plasmodium and Toxoplasma elimination
Protozoan parasites such as Plasmodium and Toxoplasma invade host cells and divide within a parasitophorous vacuole. The vacular membrane is modified by the invading parasite in order to forestall its fusion with host endocytic and degradative organelles (lysosomes). Ling et al. examined how mouse macrophages, after being infected by T. gondii, can break through this parasite-constructed defensive wall. Cells from mice lacking an interferon-inducible p47 GTPase (IGTP) failed to eliminate the pathogen. In contrast, in wild-type cells the parasitophorous vacuole membrane was disrupted during the degradation process, and the parasite plasma membrane was stripped away. The parasite was then engulfed by a double-membrane autophagosome, which fused with lysosomes, leading to destruction of the parasite. Recently, IGTPs have been shown to play a similar role in the elimination of intracellular Mycobacterium in mice and in humans.

J Exp Med 2006;203:2063
Eitan Israel