SHORT REPORTS

Association of placenta praevia and sex ratio at birth

MacGillivray *et al* reported a significant increase in the proportion of male infants born to women with placenta praevia.[1] They concluded that late fertilisation may be a predisposing factor to placenta praevia because the male to female ratio is said to be increased when fertilisation occurs late in the menstrual cycle.[2] We undertook the present study to explore the relation between placenta praevia and sex, taking parity and other factors into account.

Methods and results

We used data from the collaborative perinatal project and the National Institute of Child Health and Human Development-Kaiser Permanente birth defects study to determine the relation between placenta praevia and sex ratio. We were therefore able to look for the reported increase in male births in two independently collected samples and, by combining the two, increased our power to detect true differences in the sex ratio. The protocols of both studies are described elsewhere.[3,4] The collaborative perinatal project was a prospective study conducted in 12 university centres during 1959-66. The birth defects study was a prospective perinatal study conducted at a large health maintenance organisation during 1974-7.

Logistic regression was used to test for trend in sex ratio with increasing parity. The Pearson χ^2 statistic was used to test for independence of sex ratio and parity.

The table shows the number of cases of placenta praevia and the ratio of male to female infants stratified by parity for each study separately and for both combined. The overall incidence of placenta praevia in the collaborative perinatal project (4·1/1000) was comparable with that in the birth defects study (4·0/1000). As expected, this incidence increased significantly with increasing parity ($p<0·001$). The sex ratio among all cases of placenta praevia was 0·937 (95% confidence interval 0·716 to 1·226) in the collaborative perinatal project, 0·925 (0·652 to 1·311) in the birth defects study, and 0·933 (0·755 to 1·154) in the two studies combined. For the entire study population the sex ratio did not increase significantly with increasing parity ($p=0·30$). Among the cases of placenta praevia there was no significant association between sex ratio and parity shown by the Pearson χ^2 test in either study or when the two were combined. There was no significant trend of increasing sex ratio with increasing parity (collaborative perinatal project $p=0·42$, birth defects study $p=0·85$, combined $p=0·76$). These findings did not change significantly when the analysis was repeated for white women and non-white women separately or when multiple births were included. The collaborative perinatal project also collected data on low placental implantation, defined as a placenta located within one finger length of the os: including these women among those with placenta praevia did not alter the results.

When a study fails to confirm a reported result it is important to show that the failure was not due to inadequate power. This study had a power greater than 0·99 to detect the difference in the sex distributions of infants born to mothers with and without placenta praevia found in the ridit analysis of MacGillivray *et al*.

Comment

The suggestion by MacGillivray *et al* that late fertilisation increased the risk of placenta praevia was disturbing because of the well known association between placenta praevia and both perinatal death and low birth weight.[4] The postulated relation depended on their findings of altered sex ratios and on the assumption that the observed increase in male births resulted from late fertilisation. We cannot comment on the validity of the assumption; however, placenta praevia was not associated with a higher ratio of male to female infants in either of the studies we examined. This should reassure clinicians and women who conceive "late." Our findings suggest that the results of MacGillivray *et al* were due to chance. Moreover, they provide strong evidence against the hypothesis that late conception is linked to placenta praevia.

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Tolerance to glyceryl trinitrate patches: prevention by intermittent dosing

Long acting nitrates are widely used to treat angina with the objective of providing continuous antianginal prophylaxis, but there is growing evidence that sustained raised nitrate concentrations may lead to tolerance.[1-4] We report an investigation that assessed the extent of tolerance during continuous and intermittent treatment with glyceryl trinitrate patches.

Patients, methods, and results

Twelve patients took part in the study, which comprised two sequential double blind crossover phases: the first assessed short term antianginal efficacy and the second compared long term efficacy during continuous and intermittent treatment. In the first phase exercise testing was performed before and three and a half hours after application of an active (10 mg, Transiderm-Nitro) or placebo patch. In the second phase patients received intermittent or continuous treatment for one week, had a three day washout period, and then crossed over to the alternative treatment. Patches were changed twice daily at 0800 and 2000. During continuous treatment both morning and evening patches were active; during intermittent treatment the morning patch was active and the evening patch a placebo. Exercise testing was repeated on the eighth day of each treatment period before and three and a half hours after application of an active patch.

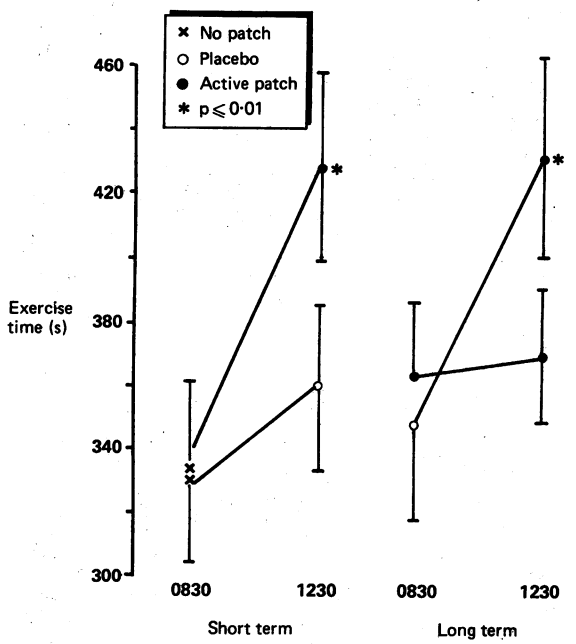
Exercise testing was performed on a treadmill (Bruce protocol). ST segment depression was measured at peak exercise and at the maximum exercise time achieved in all of a patient's tests—that is, at maximum common workload.

Ratio of male to female infants by parity among women with and without placenta praevia

Parity	Placenta praevia	Collaborative perinatal project		Birth defects study		Combined total	
		No	Male:female ratio	No	Male:female ratio	No	Male:female ratio
0	Yes	20	1·500	41	1·278	61	1·346
	No	15 982	1·040	14 371	1·058	30 353	1·049
1	Yes	42	0·680	52	0·733	94	0·709
	No	12 118	1·024	11 438	1·079	23 556	1·050
2	Yes	36	0·714	20	0·818	56	0·750
	No	8 691	1·030	4 325	1·069	13 016	1·043
3	Yes	29	1·071	6	1·000	35	1·059
	No	5 947	1·027	1 346	1·164	7 293	1·051
4	Yes	35	1·188	5	0·250	40	1·000
	No	3 960	1·036	470	1·176	4 430	1·050
≥5	Yes	53	0·963	5	4·000	58	1·071
	No	6 334	1·024	356	1·145	6 690	1·030
Total	Yes	215	0·937	129	0·925	344	0·933
	No	53 032	1·031	32 306	1·074	85 338	1·047

Patients had a history of classical, stable, exertional angina; a previous positive exercise test; and proved responsiveness to nitrates (exercise time prolonged by at least one minute after sublingual glyceryl trinitrate). No patient had previously taken long acting nitrates, and no nitrates other than sublingual glyceryl trinitrate were taken during the study.

In the study of short term efficacy the active patch prolonged exercise time by 68 seconds compared with the placebo (95% confidence interval 24 to 111 seconds, $p<0.01$) (figure). In the long term phase (0830 tests) there was no significant difference in exercise time during continuous active treatment compared with the placebo period of intermittent treatment. By contrast, during the active period of intermittent treatment (1230 tests) exercise time was prolonged by 62 seconds (confidence interval 18 to 105 seconds, $p=0.01$) compared with continuous treatment.



Mean (SEM) results of exercise testing in short term and long term studies of glyceryl trinitrate treatment. In the short term phase patients underwent exercise testing at 0830, received a patch at 0900, and were retested at 1230. In the long term phase patients underwent exercise testing at 0830 with the previous evening's patch in position (comparison between continuous active treatment and placebo period of intermittent treatment); received an active patch at 0900; and were retested at 1230 (comparison between continuous active treatment and active period of intermittent treatment).

In the short term phase ST depression at maximum common exercise time was significantly reduced after application of an active patch compared with placebo (difference=0·36 mm, confidence interval 0·16 to 0·55 mm, $p<0.01$). In the long term phase no difference was observed between continuous active treatment and the placebo period of intermittent treatment. By contrast, during the active period of intermittent treatment a reduction in ST depression still occurred (difference 0·37 mm compared with continuous treatment; confidence interval 0·07 to 0·68 mm, $p<0.05$). At peak exercise there was no significant effect on ST depression in either phase.

There was no evidence of exacerbation of anginal symptoms during overnight placebo treatment in the intermittent phase (1·0 (SEM 0·5) episode/patient week with intermittent treatment; 1·0 (0·5) with continuous treatment).

Comment

Our results support previous studies which showed that a high degree of tolerance develops during continuous use of glyceryl trinitrate patches.[4,5] The prolonged exercise time and reduced ST depression at maximum common workload that occurred with short term administration were virtually abolished after one week of continuous treatment. By contrast, tolerance did not occur during intermittent treatment and beneficial effects were maintained.

There was no evidence of exacerbation of anginal symptoms overnight, when no nitrate was being supplied. Nevertheless, we are wary of extending our conclusions to all patients with angina, particularly those with angina decubitus.

The problem of nitrate tolerance is not confined to patch treatment, and the implication for all nitrate preparations is that dosage regimens should be tailored to each patient to provide protection at times of maximum susceptibility. Attempted 24 hour protection may be self defeating.

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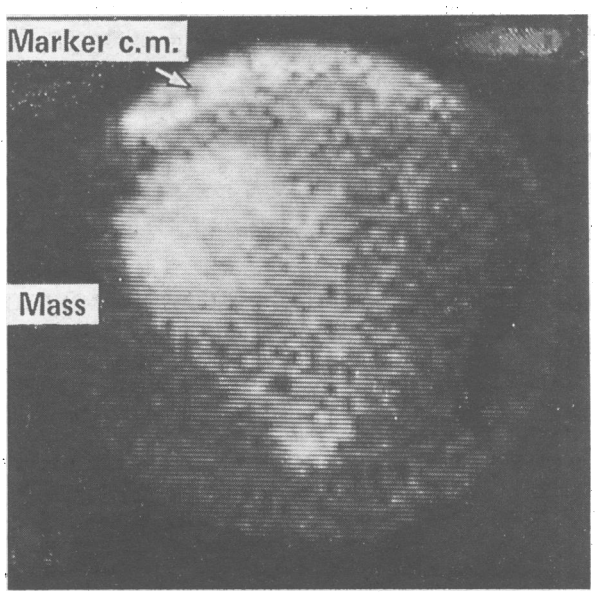
Immunoscintigraphy of metastases with radiolabelled human antibodies

A lymphoblastoid cell line, secreting human immunoglobulin, has been produced by transformation of lymph node lymphocytes, recovered at operation for pancreatic adenocarcinoma, using Epstein-Barr virus.[1] Specific antibody secreting clones were selected by testing the supernatants from the lymphoblastoid cells against the same tumour cells and other cell lines, using a modified enzyme linked immunosorbent assay (ELISA) with the cells adherent to microtitre plate wells.[2] In addition, antibody specificity was confirmed by lack of binding to various cell lines: with *o*-phenyldiamine as substrate the mean value of five spectrophotometric determinations of binding of the human antibody to the pancreatic adenocarcinoma cells was 0·973 (SD 0·129) compared with 0·153 (0·088) for all other cell lines assessed.[3] The antibody was shown to be of the IgG class and was labelled with iodine-131 by the "iodogen" method.[4] We used this human antibody to assess the extent of a growth in a patient with secondary disease.



Radioimmunoscintigram: anterior view of abdomen at 20 hours. A focal area of increased uptake is seen just below the liver area (mass). A marker was placed over the costal margin (c.m.).

Case report

A 54 year old woman had undergone a Whipple's operation 10 months previously for a pancreatic adenocarcinoma, which had been histologically classified as a poorly differentiated carcinoma. After clinical diagnosis of hepatic secondaries she was admitted to the surgical unit for further investigations. Ultrasonography showed the presence of a large solid tumour associated with the