Induction of labor with vaginal prostaglandin-E2 in women with one previous cesarean section

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Induction of labor is considered necessary in certain clinical situations. These include postdate pregnancy, term premature rupture of membranes, preeclampsia, intrauterine growth retardation, and significant medical diseases such as diabetes mellitus at term. Intravaginal or intracervical dinoprostone (prostaglandin-E2 [PGE2]) is the most used pharmacologic method to ripen the cervix and induce labor. Cervical ripening and labor induction in women with one previous low transverse cesarean section (CS) is controversial. The objective of this study was to assess the safety and effectiveness of induction of labor with vaginal PGE2 in candidate women for vaginal birth after cesarean (VBAC).

From January 1995 to December 2000, there were 510 induction of labor with vaginal PGE2 (dinoprostone; ProstinTM E2, Upjohn, London, United Kingdom) at King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia. The outcome of induction of labor with vaginal PGE2 (3 mg tablet every 6 hours for a maximum of 3 doses) in 41 women with one previous low transverse CS was compared to the outcome of spontaneous labor of 82 women with one previous CS matched for age, parity, and gestational age at delivery. There was no statistical significant differences in the duration of labor, fetal birth weight, estimated blood loss at delivery, and Apgar scores in the 2 groups. In the induction group, 27 (65.9%) women delivered vaginally and 14 (34.1%) women by emergency cesarean section (ECS). In the control group, 58 (70.7%) women delivered vaginally and 24 (29.3%) women by ECS. However, in the induction group the mean duration of the hospital stay of the mother was longer (p = 0.019) and there was one (2.4%) asymptomatic uterine dehiscence discovered at CS compared to one (1.2%) in the control group. Both cases of asymptomatic uterine dehiscence of the CS scar were easily repaired and no hysterectomy was performed. In a review of 10 studied published in 2000,[1] the incidence of uterine scar disruption was not differ from women who received PGE2 and women who entered labor spontaneously (1.6% versus 1.23%, odds ratio of 1.46, 95% confidence interval 0.96-2.22). However, more recent studies showed an increase in the uterine rupture and decreased vaginal delivery rates with induction with PGE2.[2,3] The American College of Obstetrics and Gynecologist[4] based on limited or inconsistent scientific evidence recommended that the use of prostaglandin gel for VBAC "requires close patient monitoring". It has been shown repeatedly from many studies of VBAC that one of the important prognostic factors for success is history of previous vaginal delivery. This was not carried out in other studies. Our findings suggest that induction of labor with PGE2 in women candidates for VBAC is effective and may be safe. However, the couple should be counseled on the potential increased risk of uterine scar dehiscence or rupture.

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The association of acute myocardial infarction and pregnancy loss in young female with primary antiphospholipid syndrome

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Acute arterial and venous thrombosis is a common manifestation of antiphospholipid syndrome.[1] Acute myocardial infarction may be a clinical manifestation in young adults.[2] Pregnancy in women who are positive for antiphospholipid antibodies may have recurrent pregnancy loss.[3] We describe a young female with no history of venous thrombosis, presented with an incomplete abortion with complicated acute myocardial infarction, thrombolytic therapy was given with no complications. Her blood test was positive for antiphospholipid antibody and the case proved to be primary antiphospholipid syndrome.

A 21-year-old female patient of 10 weeks gestation presented with 2 days history of mild vaginal bleeding and fever. She was admitted to the hospital and managed with intravenous (I.V.) fluid and I.V. metronidazole and amoxicillin clavulanate. She was planned for dilatation and curettage in <24 hours in the hospital, but she developed acute retrosternal chest pain followed by dyspnea, oxygen desaturation of 85%. She developed acute pulmonary edema clinically and radiologically. The 12 leads electrocardiogram showed acute ischemic changes with ST segment elevation of 2 mm. At leads I, III and a augmented unipolar left leg lead with reciprocal ST segment depression at precordial and lateral leads. Clinical examination revealed blood pressure of 95/60 mm Hg, heart rate of 110 beat per minute, respiratory rate of 24 beat per minute and temperature of 37.70C. Chest with fine bibasal rales and S3 gallop with soft systolic murmur of 2/6 in the apical area. Laboratory blood result showed white blood cell of 8000/uL, hemoglobin of 10 gm/dl, and platelet of 345,000/uL. Peaked creatinine kinase isoenzyme of 132 U/L, total creatinine kinase of 1990 U/L and aspartate aminotransferase of 148 U/L, alanine aminotransferase of 70 U/L, urea of 8 mmol/L, creatinine of 90 umol/L, bilirubin 12 umol/L, alkaline phosphatase of 124 U/L, albumin of 40 g/L, globulin 30 g/L, cholesterol 4.2 mmol/L, triglyceride 2.1 mmol/L, international normalized ratio (INR) of 1.5, activated partial thromboplastine time 52 per second, complement C3 of 0.02 mg/dl (N = 0.2-0.5), C4 of 0.5 mg/dl (N = 0.5-1.2). Antiphospholipid antibody and anticardiolipin antibody were both positive. Antinuclear factor (ANF) was positive. Anti-double strand DNA antibody and smooth muscle antibodies were negative. Furosemide and dopamine I.V. infusion at 3 ug/kg per minute were given. Streptokinase I.V. infusion of 1.5 million units administered over one hour. Post thrombolytic electrocardiogram showed reduction of ST amplitude in inferior leads and normalization of precordial leads in favor of successful thrombolytic therapy. Echo showed inferior wall hypokinesia, mild mitral regurgitation, no echo dense masses seen. Left ventricle wall and cavity dimensions were normal, overall left ventricle ejection fraction of 45%. Coronary angiography showed no atheromatous narrowing in the left anterior descending or the left circumflex artery or the right coronary artery. She had unremarkable hospital recovery and underwent dilation and curettage later with no complications. She was discharged and maintained on long term Aspirin 100 mg daily and oral anticoagulant to keep INR of 2-3. The most common manifestation of antiphospholipid syndrome is deep venous thrombosis of the leg; half of these patients develop pulmonary emboli. Arterial thromboses are less common than venous thromboses and manifest with ischemia or infarction. The brain is the most common site of arterial thrombosis with stroke and transient ischemic attacks, account for 50% of arterial occlusion, coronary artery occlusion account for 23%; other sites are the subclavian, renal, retinal and pedal arteries.[4] In this case, a young female presented for the first time with incomplete abortion complicated with acute inferior myocardial infarction. She was diagnosed as primary antiphospholipid antibody syndrome, as the blood assays were positive for antiphospholipid antibody and anticardiolipin antibody. Primary antiphospholipid syndrome is one of several prothrombotic states that occur in young patients, in which recurrent thrombosis can occur with both venous and arterial beds. The administration of thrombolytic therapy although is debatable in proven cases of primary antiphospholipid syndrome due to the high risk of bleeding, was given successfully in this case, with no bleeding complication that, in keeping with others who had reported the safe administration of thrombolytic therapy in a similar case.[5] Primary coronary angioplasty is regarded as a superior alternative to thrombolytic therapy in such case, but it was not contemplated due to the lack of accessibility. The absence of atheromatous narrowing in the precordial artery on angiography indicated the likelihood of arterial thrombus as a cause of acute myocardial infarction that probably dissolved by thrombolysis. So in the clinical setting where a young patient presented with pregnancy loss and acute myocardial infarction, screening for antiphospholipid antibody as an attributable factor with other assays that are sensitive for lupus anticoagulant antibodies is mandatory, as the long term line of management is different.

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Diclofenac suppositories in the treatment of bone and joint diseases. *A forgotten route*

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Rectal administration of any drugs is resented by people of all cultures for psychomythical fear that its habitual use will lead to homosexuality, loss of manhood, and interference in the course of nature dictating the anus as an "exit only" opening. On the other hand, females accept vaginal ovules and pessaries as nature dictates dual function of the vagina canal in intercourse and labor. As a patient I would like to share with your readership my experience and that of the orthopedic and rheumatology units of Salmaniya Medical Complex (SMC), Bahrain in the treatment of bone and joint disease using Diclofenac Sodium suppositories.

In 1999, I developed right hip pain diagnosed by magnetic resonance imaging as Bone Marrow Edema syndrome (or transient osteoporosis) involving upper femur but not extending into the neck or head. Physiotherapy together with paracetamol and Celecoxib 200 mg/day were tried for 2 weeks with no pain relieve. As a result of the pain and restriction of leg movements, wasting of the quadriceps muscle developed. Surgical interference to relieve the femoral intramedullay edema pressure was ruled out for fear that the post-operative immobilization will worsen the muscle wasting and that any weight bearing movements will lead to fracture. Subsequently when Diclofenac Sodium 100 mg/day retard capsules were given, pain was relieved within 30 minutes of ingestion and the effect lasted for approximately 10 hours. Paracetamol controlled the pain during the remaining part of the day. With this protocol physiotherapy was possible. However, after 11 days, melena developed indicating direct prostaglandin inhibitory effect of Diclofenac on the gastric mucosa.[1] Diclofenac discontinued and Omeprazole 20 mg per day and other conservative measures were given. At this stage the surgeons deliberated to prescribe other non-steroidal anti-inflammatory drug (NSAID) and considered decompression of the edema or hip replacement once the edema extends into the femoral head. The patient who refused to sacrifice a femoral head for the sake of pain did not favor this. Three factors were considered: (1) The crucial determinant in management was to break the cycle of pain which led to restriction of limb movement and subsequently further muscular wasting, progression of osteoporosis, and more pain. (2) The hip replacement will still leave the bone marrow edema untreated. (3) The post-operative period require weight bearing exercise and this may lead to fractures. As a patient (with reasonable knowledge of medicine), I began to investigate other options. Diclofenac was an effective drug and to circumvent its prostaglandin inhibitory effect on the gastric tissue other routes of administration were considered. The clinicians were unaware that the preparation is available in the form of suppositories, which I successfully used leading to symptomatic relieve within 6 weeks. The pain was relieved after the administration of 12.5 mg pediatric suppositories was felt within 30-45 minutes lasting for up to 5 hours. Up to 4 suppositories were administered per 24 hours depending on the severity of pain thus ensuring comfort throughout the day. With pain relieve, quadriceps strengthening with physiotherapy was possible and this gradually decreased the osteoporosis thus breaking up the above cycle. Magnetic resonance imaging was carried out 18 months after pain relieve showed normal bone density. This experience prompted the clinical practitioners at the rheumatology and orthopedic units of SMC to routinely prescribed pediatric suppositories to their adult patients who also suffer from gastric intolerance to NSAID. The results were remarkably positive.

There is a substantial first pass effect after oral Diclofenac with only about 50% of the drug available systematically.[1] This effect is totally bypassed with rectal administration. Arguably, applying the same ratio while considering that two thirds of the rectal venous drainage is portal (superior and middle rectal veins) and one third systemic (inferior rectal vein) at least 66% of the drug will be available systematically after rectal administration. The 12.5-mg pediatric suppositories are small and well tolerated by adults and readily absorbed within <1 hour. The cost of each suppository is 6 p whereas that of a capsule is 33 p.[2] This means that the cost of 4 suppositories with therapeutic effect lasting for 24 hours is 9 p cheaper than the effect of the capsule, which last for 10 hours.

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Trend of antibiotic resistance in 1316 *Shigella* strains isolated in Bahrain

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It is estimated that *Shigella* is to blame worldwide for 600,000 deaths per year, 60% of which occur in children. Investigating the evolutionary relationships of *Shigella*, it was found[1] that they are within the *Escherichia coli* (*E coli*), not representing a genus by them. Probably they evolved within the last 35,000 - 270,000 years, one of the early infections afflicting humans. *Shigella sonnei* (*S. sonnei*) and *Shigella flexneri* (*S. flexneri*) are the most common isolated organisms but *Shigella dysenteriae* (*S. dysenteriae*) is responsible for the most severe cases. *Shigellosis*, differently from other diarrheal diseases for which fluid replacement therapy can be usually considered satisfactory, represents a major indication for antimicrobial therapy. All over the world reports of multiple drug resistance are well documented,[2] as well as in the Middle East.[3,4] Although percentages vary in the different studies from various areas, reflecting different epidemiology and antibiotic usage, comparisons over subsequent years show a consistent increase in resistance over time.

We report our experience on antibiotic susceptibilities during the period 1994-2001 on a total of 1316 strains all isolated from stools, comparing the obtained results with relevant data gathered in the period 1984-1988. Stool specimens were inoculated on deoxycholate agar (DCA), selenite broth, subcultured on DCA and incubated at 37°C for 24 hours. Suspected colonies were further biochemically tested and serogrouped by the slide agglutination test (Murex Biotech LTD, England). In vitro, antibiotic sensitivity testing was performed by the standard disc (Mast, England) diffusion method. Interpretation criteria were according to the National Committee for Clinical Laboratory Standards (NCCLS) manual. The quality control organism was *E coli* american type culture collection 25922. The highest number of isolates was observed for *S. sonnei* (664 strains; 50.5%), followed by *S. flexneri* (450 strains; 34.2%). The lowest number of isolates was detected for *Shigella boydii* (*S. boydii*) (122; 9.3%,) presenting a peak in 1994, and *S. dysenteriae* (80 isolates; 6.1%), with a disquieting peak in 2000. The isolation rate for the different species did not change over a long period of time. A previous investigation from our Laboratory[4] covering the period 1984-1988 showed *S. sonnei* most abundant (48%), followed by *S. flexneri* (40%), *S. boydii* (8.4%), and *Shigella dysenteriae* (3%). Thus, the relative incidence of various species is constant during a long periods. Isolation rates were higher in children (below 15 years of age) showing modest variations during the period investigated (70.8-74.8%). No increasing trend in the number of cases was noted. From **Table 1**, it is evident that in the last 3 years, stable values for resistance to chloraphenicol (CAF), co-trimoxazole (SXT) and ampicillin (AMP), were recorded. More relevant is the dramatic increase (but it can represent, a worrying peak,) in resistance to Cefuroxime. These data was obtained from 108 strains tested and not from all isolates. This antibiotic was tested as it is widely used by pediatricians, who cannot rely on ciprofloxacin, as it is not approved for use in children. From **Table 2**, where data was arranged for different subgroups, it is apparent that resistance to the various antibiotics tested varies according to the different species. *S. sonnei* shows the uppermost resistance to SXT (range 77.2-98%) similar to what was observed for *S. flexneri.* All strains were found sensitive to ciprofloxacin and ceftriaxone. Sensitivity to cefotaxime and to ceftriaxone indicates that the plasmid described coding for an extended spectrum beta-lactamase (ESBL) is not yet present in our region. Resistance to cefuroxime (a surprising peak of 20% in 2000 for *S. boydii* and of 63.6% for *S. dysenteriae* in 2001) is a very alarming and needs to be investigated further. However, the most striking result is the trend of resistance over the years for the 2 most commonly isolated subgroups. Regarding *S. sonnei*, no increasing trend in resistance was found: AMP is at its lowest in 2000 with values in 2001 lower than those observed in 1994 and SXT appears constant at a very high percentage. The very low CAF resistance rate is equal to what it was 8 years ago. In *S. flexneri* resistance to AMP is significantly declining, from the peak observed in 1996 (95%) down to 54.7% in 2000, showing a further significant decrease to 52.6% in 1999. A similar trend is shown for SXT, decrease from 83.4% in 1994 to 52.8% in 2000. A similar pattern is also observed for CAF, now on a value of 44.4% compared to the peak of 90% in 1996 and the average of 78.5 % over the period 1995-1998. Intriguingly enough, this trend is not to be observed with other subgroups where the number of resistant strains isolated was erratic during the years. The only increasing trend is related to resistance to cefuroxime for *S. flexneri*, which can only represent an isolated peak rather than a consistent climb. Comparing the percentage of antibiotic resistant strains tested in the year 1987-1988[13] and 2000, it is evident that different species behave in different ways. However, a trend for decrease or no change was observed for *S. flexneri* and *S. boydii*, while for *S. sonnei* a minor increase was found for CAF resistance while a decrease was detected for ampicillin. The only species showing a uniform tendency to increased resistance was *S. dysenteriae*, the least common isolate. We can conclude that the profile of resistance is variable in the diverse species and that antibiotic resistance in all *Shigella* subgroups, at least in our region, is not on the

Table 1 - *Shigella* species strains (%) resistant to the tested antibiotics (N = 1,316).

Antibiotics	2001 N = 118	2000 N = 195	1999 N = 121	1997 N = 186	1996 N = 219	1995 N = 103	1994 N = 204
Ampicillin	38.4	32.3	24.8	52.2	36	39	51.5
Ceftriaxone	0	0	0	0	0	0	0
Cefuroxime	11.1*	26.2	NT	0.5	6	0	1.5
Cefotaxime	0	0	0	NT	NT	NT	NT
Co-trimoxazole	59.3	65.5	66.1	89.3	87	76.7	72
Chloramphenicol	27.1	28.8	19.8	32.3	28	30	35.3
Ciprofloxacin	0	0	0	0	0	0	0

*only 108 strains have been tested, NT - not tested

Table 2 - Resistance of different *Shigella* species to routinely tested antibiotics (N=1,316).

Strains resistant to the tested antibiotics	Ampicillin %	Ceftriaxone %	Cefuroxime %	Cefotaxime %	Co-trimoxazole %	Chloramphenicol %	Ciprofloxacin %
S. sonnei (N = 664)							
2001 n = 44	11.3	0	1.3	0	77.2	4.5	0
2000 n = 98	5.1	0	1.4	0	85.7	3.7	0
1999 n = 67	8.9	0	NT	0	80.6	0	0
1998 n = 97	6.2	0	0	0	88.6	2.1	0
1997 n = 103	28.1	0	0	0	94.2	0.97	0
1996 n = 135	6	0	2	NT	98	2	0
1995 n = 51	5.9	0	0	NT	88.2	3.9	0
1994 n = 69	14.5	0	0	NT	88.4	4.3	0
S. flexneri (N = 450)							
2001 n = 47	55.3	0	4.8	0	63.8	44.7	0
2000 n = 53	54.7	0	16.6	0	52.8	38	0
1999 n = 38	52.6	0	NT	0	60.5	57.9	0
1998 n = 60	68.3	0	0	3.3	75	76.6	0
1997 n = 72	83.3	0	1.4	NT	82	76.4	0
1996 n = 58	95	0	2	NT	81	90	0
1995 n = 38	76.3	0	0	NT	78.9	71	0
1994 n = 84	80	0	1.2	NT	83.4	66.6	0
S. boydii (N = 122)							
2001 n = 14	42.8	0	0	0	28.6	21.4	0
2000 n = 21	61.9	0	20	0	23.8	0	0
1999 n = 9	33.3	0	NT	0	22.2	22.2	0
1998 n = 9	33.3	0	0	0	44.4	33.3	0
1997 n = 8	62.5	0	0	NT	87.5	25	0
1996 n = 16	62	0	25	NT	44	19	0
1995 n = 7	57	0	0	NT	28.6	0	0
1994 n = 38	50	0	0	NT	31.6	23.6	0
S. dysenteriae (N = 80)							
2001 n = 13	69.2	0	63.6	0	15.4	61.5	0
2000 n = 23	59.6	0	5.5	0	47.8	71.4	0
1999 n = 7	14.3	0	NT	0	14.3	0	0
1998 n = 4	75	0	NT	0	50	0	0
1997 n = 3	100	0	0	NT	100	66.6	0
1996 n = 10	40	0	10	NT	40	30	0
1995 n = 7	57	0	0	NT	28.6	28	0
1994 n = 13	69.2	0	5.4	NT	30.8	30.8	0

S - *Shigella*, NT - not tested

rise but shows wide fluctuations over the years recorded. Our data, in view of the long period examined, can be compared with the data collected at the International Center for Diarrheal Disease Research in Bangladesh (ICDDR B).[5] In respect to the AMP report from ICDDR B, it shows an increase in resistance up to 90% in 1988 for *S. dysenteriae*, while in our experience a maximum of 100% was obtained in 1997 with a decrease to 60% in 2000. Considering all *Shigella species*, our current resistant rate is equal to 38.4%, similar to the values reported by ICDDR B in 1985. Comparing the current data with a previous study that was carried on from our institution, rates for AMP were unchanged; for *S. sonnei* 9.2% in 1987-1988 versus 8.2% in 2000-2001, for *S. boydii* 61% in 1987-1988 versus 52.3% in 2000-2001, and for *S. dysenteriae* 58% in 1987-1988 versus 64.4% in 2000-2001. A significant reduction from 75.6% in 1987-1988 to 55% in 2000-2001 was detected for *S. flexneri*. The data from ICDDR B for cotrimoxazole show that an increase was observed for all *Shigella* groups, from 20% in 1983 to 60% in 1991. Our data show a decrease from the peak was observed in 1997 (89.3%) to the current values, approximately 60%. A composite picture emerges from the comparison of present results with previous ones at our institution in the years 1987-88. While for *S. sonnei* there is an increase when compared with 2000-2001 (24.5-81.4%), an opposite trend has been detected for *S. boydii* and *S. dysenteriae* (with a decrease from 51% to 26.2% and from 40% to 31.6%). It is reported that, particularly in developing countries, quinolone resistance is on the rise.[5] We did not isolate a single strain resistant to ciprofloxacin, indicating that factors favoring the appearance of the chromosomal mutation involved in this type of resistance, are not operating in our population. More worrisome is the TEM-1 beta-lactamase mediated increase in resistance to cefuroxime, most likely associated with plasmid-encoded beta-lactamase production.[5] Interestingly ceftriaxone and cefotaxime retained their activity on all isolates. From this long term analysis it seems that when, for diverse reasons, antibiotic selective pressure is reduced, bacteria can revert to sensitivity. This propensity can be exploited in a rational and planned way to make again efficacious old, safe and less costly antibiotics.

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