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ALGAZI M., PLU-BUREAU G., FLAHAULT A., DONDON M.G., LE M.G.

Could treatments with beta-blockers be associated with a reduction in cancer risk?

Rev. Épidémiol. Santé Publ., 52 (1), 53-65, 2004

(Services cités : Endocrinologie & Médecine de la Reproduction, URC)

BACKGROUND: The relationship between the use of anti-hypertensive drugs and cancer risk remains controversial. The main objective of this study was to assess the potential effect of beta-blocker use on cancer risk. **METHODS:** In a cohort of 839 patients with cardiovascular disease, followed up prospectively for an average period of 10 years, cancer occurrence was recorded according to the exposure to beta-blockers. The relative risk of cancer associated with beta-blocker use was estimated using a Cox model adjusted on gender and age. Ever- vs never-use of beta-blockers and duration of exposure to the drug were analyzed as time-dependent variables. In addition, the standardized incidence ratios (SIR) were calculated using the corresponding age- and gender-adjusted cancer incidences in the French general population. **RESULTS:** A total of 326 beta-blocker users and 513 users of other treatments were included in the cohort. During the follow-up period, representing 8,466 person-years, incident cancer cases were 15 and 59 in beta-blocker ever-users versus never-users, respectively. Using the Cox model, the overall relative risk of cancer was 0.51 (95% confidence interval [95% CI]: 0.29-0.90) in the beta-blocker ever-users versus never-users ($p=0.02$), with a 6% decrease per year of use (95% CI: 1%-12%; $p=0.03$). The corresponding SIR ratio between these two groups was 0.44 (95% CI: 0.24-0.76).

CONCLUSION: In this cohort, the beta-blocker treatments appeared to decrease the cancer risk significantly. However, this result should be considered with caution; further work is needed, as some sources of bias associated with this type of epidemiological study cannot be totally excluded.

ALHENC-GELAS M., PLU-BUREAU G., GUILLONNEAU S., KIRZIN J.M., AIACH M., OCHAT N., SCARABIN P.Y.

Impact of progestagens on activated protein C (APC) resistance among users of oral contraceptives.

J. Thromb. Homeost., 2 (9), 1594-1600, 2004

(Services cités : URC)

Oral contraceptive (OC) use is associated with an increased risk of venous thromboembolism. Previous data reported higher thrombotic risk in women using third-generation combined OC than in those using second generation OC. The difference could be explained by differential effects of progestagens on plasma sensitivity to activated protein C (APC). The main purpose of this cross-sectional study was to assess the influence of a progestagen-only OC (chlormadinone acetate) as well as the effect of several combined OC with different progestagen components on APC resistance. The effect of APC on endogenous thrombin potential (ETP) was investigated in the plasma of healthy women using either combined OC ($n=82$) or progestagen-only OC ($n=28$), and in non-users ($n=64$). Carriers of factor V Leiden were excluded. Compared with non-users, there was no significant change in APC resistance in women using progestagen-only OC. Women who used combined OC were less sensitive to APC than non-users ($P < 0.001$) and the difference

was significantly more pronounced in women using third-generation OC (n=41) than in those who used second-generation OC containing levonorgestrel (n=22) ($P < 0.05$). Compared with OC containing levonorgestrel, use of norethisterone-containing OC (n = 9) was associated with an increased resistance to APC ($P < 0.05$). Women who used cyproterone-containing OC (n = 10) were less sensitive to APC than those using third-generation OC ($P < 0.05$) or second-generation OC containing levonorgestrel ($P < 0.05$). Protein S, factor II and FVIII levels explained in part the OC-related changes in APC sensitivity variations. ETP-based APC resistance may contribute to explain why different brands of OC can be associated with different levels of thrombogenicity.

CONARD J., PLU-BUREAU G., BAHI N., HORELLOU M.H., PELISSIER C., THALABARD J.C.

Progestogen-only contraception in women at high risk of venous thromboembolism.

Contraception, 70 (6), 437-441, 2004

(Services cités : Endocrinologie & Médecine de la Reproduction, URC)

The objective of the study was to evaluate the venous impact of a progestogen-only contraception on women at high risk of venous thromboembolism (VTE). In this retrospective cohort study, 204 consecutive women at high risk of VTE were recruited between January 1992 and June 1997 and were prospectively followed. Women using chlormadinone acetate (CMA) at antigonadotropic doses (n=102) were matched by age and date of referral and history of venous thrombosis with women who had no hormonal contraception (n=102). During follow-up (mean of 33 months), nine episodes of VTE were observed: three in women receiving CMA and six in nontreated women. Using the Cox model to adjust for confounding variables such as age, thrombophilia and body mass index, the relative risk of VTE associated with the use of CMA was not significant [relative risk: 0.8 (0.2-3.9)]. These reassuring results need to be confirmed in other prospective studies.

LEVY D., PLU-BUREAU G., DECROIX Y., HUGOL D., ROSTENE W., KIMCHI A., GOMPEL A.

Death-associated protein kinase loss of expression is a new marker for breast cancer prognosis.

Clin. Cancer Res., 10 (9), 3124-3130, 2004

(Services cités : URC)

PURPOSE: Death-associated protein (DAP)-kinase is a new Ser/Thr kinase involved in cell apoptosis and tumor suppression, the expression of which has been correlated to invasive potential and metastasis in several human neoplastic tissues. We analyzed the level of DAP-kinase expression in breast cancer specimens and its correlation with survival. **EXPERIMENTAL DESIGN:** One hundred twenty-eight breast cancer specimens were analyzed by immunohistochemistry. Patient records were studied retrospectively for demographic characteristics, clinical data, hormonal treatment, outcome, and survival. DAP-kinase protein expression was also studied in normal breast cells primary cultures under estrogen and antiestrogen treatment. **RESULTS:** Among the 128 patients, 30 showed a DAP-kinase staining $< \text{or} = 20\%$, whereas 98 had a staining over 20%. Mean follow-up time was 62 months. The association between tumor Scarff-Bloom and Richardson grade ($P = 0.009$), estrogen receptor and progesterone receptor expression ($P = 0.002$ and 0.001 , respectively), tumor size ($P = 0.05$), Bcl-2 expression ($P = 0.004$), and DAP-kinase immunostaining in the ductal carcinoma group was highly significant. Overall (64 months) and disease-free (63 months) survival in the high DAP-kinase expression group were significantly longer compared with the women whose tumors showed a loss of DAP-kinase expression (51 and 43 months, respectively). DAP-kinase protein

was strongly expressed in normal breast tissue and in human breast epithelial cells primary cultures. Estradiol decreased DAP-kinase expression in these cells, arguing for hormonal regulation of the protein. CONCLUSIONS: Loss of DAP-kinase expression negatively correlates to survival and positively correlates to the probability of recurrence in a very significant manner. DAP-kinase thus constitutes a novel and independent prognosis marker for breast cancer.

MAHIEU-CAPUTO D., AUBRY M.C., EL SAYED M., JOUBIN L., THALABARD J.C., DOMMERGUES M.

Evaluation of fetal pulmonary vasculature by power Doppler imaging in congenital diaphragmatic hernia.

J. Ultrasound Med., 23 (8), 1011-1017, 2004

(Services cités : URC, Maternité)

OBJECTIVE: To evaluate the feasibility of prenatal power Doppler imaging of pulmonary arteries in congenital diaphragmatic hernia and to study its potential to predict outcome.

METHODS: A prospective observational study was conducted. Forty-two cases of congenital diaphragmatic hernia (32 left and 10 right) without associated anomalies were analyzed.

Qualitative evaluation of pulmonary vasculature was based on power Doppler imaging performed at 26 to 38 weeks. The pulmonary arteries were studied in the lung contralateral to the hernia.

Pulmonary Doppler angiography was considered satisfactory when 3 levels of bifurcation defining 3 distinct segments of the pulmonary arteries were imaged and was otherwise considered poor. We also recorded the gestational age at diagnosis, side of the hernia, abdominal circumference below the third percentile, amniotic fluid volume, lung/thoracic area ratio,

left/right ventricle ratio, and, in left-sided hernias, stomach position, and we carried out a multivariate analysis to determine the contribution of each factor to predict neonatal mortality.

RESULTS: More than 3 divisions of the fetal pulmonary arteries were imaged in 20 cases; 1 or 2 divisions or none were imaged in 22. Neonatal mortality was significantly greater when fewer than 3 divisions of the pulmonary arteries were imaged (18 [82%] of 22) than when 3 divisions could be identified on power Doppler imaging (5 [25%] of 20; $P = .0005$). However, the lung/thoracic area ratio was the only factor that remained significantly associated with mortality in the multivariate analysis. CONCLUSIONS: An altered pulmonary power Doppler image is associated with neonatal mortality, but estimation of the lung area remains the best predictor of neonatal outcome.

RUANO R., BENACHI A., JOUBIN L., AUBRY M.C., THALABARD J.C., DUMEZ Y., DOMMERGUES M.

Three-dimensional ultrasonographic assessment of fetal lung volume as prognostic factor in isolated congenital diaphragmatic hernia.

Br. J. Obstet. Gynaecol. - BJOG, 111 (5), 423-429, 2004

(Services cités : URC, Maternité, Endocrinologie & Médecine de la Reproduction)

Objective To evaluate the potential of three-dimensional ultrasound to predict outcome in congenital diaphragmatic hernia. Design Prospective observational study. Setting Tertiary care centre. Population Twelve cases of isolated congenital diaphragmatic hernia (11 left-sided, 1 right-sided) and 109 controls. Methods Fetal lung volume was assessed by three-dimensional ultrasound using the technique of rotation of the multiplanar imaging. In the control fetuses, a logistic transformation was performed to correlate fetal lung volume with gestational age, and the confidence interval was obtained with a bootstrap resampling. A mathematical equation was then obtained allowing calculation of the expected fetal lung volume as a function of gestational age.

In fetuses with congenital diaphragmatic hernia, the observed/expected lung volume ratio was compared with postnatal outcome. Main outcome measures Neonatal mortality and pulmonary hypoplasia, which was defined as lung/body weight ratios less than 0.012. Results The expected fetal lung volume was derived from the mathematical equation: Fetal lung volume (mL) = $\exp(4.72/(1 + \exp((20.32 - \text{gestational age in weeks})/6.05)))$. The observed/expected fetal lung volume ratio was significantly lower in the congenital diaphragmatic hernia group (median: 0.34, range: 0.16-0.66), than in the control group (median: 1.02, range: 0.62-1.97, $P < 0.0001$). The distribution of this ratio was significantly downshifted in the infants with congenital diaphragmatic hernia who died (median: 0.19, range: 0.18-0.66) compared with survivors (median: 0.44, range: 0.36-0.66, $P = 0.04$). The observed/expected fetal lung volume ratio was also correlated with the postmortem lung/body weight ratio. Conclusion In isolated congenital diaphragmatic hernia, fetal lung volume measurement by three-dimensional ultrasound is a potential predictor for pulmonary hypoplasia and postnatal outcome.

RUANO R., JOUBIN L., SONIGO P., BENACHI A., AUBRY M.C., THALABARD J.C., BRUNELLE F., DUMEZ Y., DOMMERGUES M.

Fetal lung volume estimated by 3-dimensional ultrasonography and magnetic resonance imaging in cases with isolated congenital diaphragmatic hernia.

J. Ultrasound Med., 23 (3), 353-358, 2004

(Services cités : Maternité, Radiologie Pédiatrique, URC)

Objective. To assess the agreement of 3-dimensional ultrasonography and magnetic resonance imaging in estimating fetal lung volume in cases with isolated congenital diaphragmatic hernia. Methods. Fetal lung volume was measured in 11 cases of congenital diaphragmatic hernia (10 left and 1 right) by 3-dimensional ultrasonography and magnetic resonance imaging. These examinations were performed during the same week. The operators were blinded to each other's results. Intraclass correlation was used to evaluate the agreement between 3-dimensional ultrasonography and magnetic resonance imaging estimations of the ipsilateral, contralateral, and total fetal lung volume. A Bland-Altman graph was plotted to detect possible discordant observations. Results. The global intraclass correlation coefficient between magnetic resonance imaging and 3-dimensional ultrasonographic measurement of fetal lung volume was 0.94 (95% confidence interval, 0.78-0.98) with no outliers observed on the Bland-Altman plot. Conclusions. There is a good agreement between 3-dimensional ultrasonography and magnetic resonance imaging for fetal lung volume estimation in cases with congenital diaphragmatic hernia.

SITRUK-WARE R., PLU-BUREAU G.

Exogenous progestagens and the human breast.

Maturitas, 49 (1), 58-66, 2004

(Services cités : Endocrinologie & Médecine de la Reproduction, URC)

The role of progestins (or progestagens) on the breast tissue remains controversial. However, according to the molecule and the duration of application, cell differentiation and apoptosis may predominate over proliferation. Progestins are also used as second-line agents for the treatment of metastatic breast cancer. In young women with benign breast disease, long-term treatment with 19-nortestosterone progestins had a trend to decrease breast cancer risk contrarily to what was observed in postmenopausal women receiving estrogens. Several compounds with progestational activity have been used for HRT. Small differences in the structure of the molecules may lead to pronounced differences in activities, some progestins exerting androgenic effects and some exerting estrogenic or glucocorticoid like activities. While most progestins do not bind to the

estrogen receptors, it has been shown that some androgenic progestins stimulate MCF7 cells proliferation while progestins derived from progesterone did not induce cell multiplication in the same cell lines. Therefore, different progestins may induce different effects on the breast cells. Whether the progestins available to date are able to bind specifically to the progesterone receptors PR-A or PR-B and whether this is of clinical relevance to breast cell proliferation is still unclear. Although the relationship between progestin use and breast cancer risk is still the subject of debate and controversy, the data reported to date suggest that 5 years of treatment carry a low risk but further duration of use increases the risk. Further studies are still needed, randomised long-term prospective studies as well as from the laboratory, especially to determine whether a sequential or continuous regimen would be preferable as far as breast-cell response and apoptosis are concerned, and what are the effects of the various molecules used for HRT.

VRAY M., GIRAULT D., HOOG-LABOURET N., PORCHER R., THALABARD J.C.

Methodology for small clinical trials.

Thérapie, 59 (.), 281-286, 2004

(Services cités : [URC](#))

2003

**DAVID-DUFILHO M., SCHUSSLER O., PERNOLLET M.G., BRUNET A.,
MILLANVOYE-VAN BRUSSEL E., LE QUAN SANG K.H., RENDU F.**

Therapeutic immunoglobulin reduces Ca²⁺ mobilization and von Willebrand factor secretion, and increases nitric oxide release in human endothelial cells.

Thromb. Haemost., 90 (6), 1046-1053, 2003

(Services cités : [URC](#))

Intravenous gamma-immunoglobulin (i.v.Ig) is commonly used in the treatment of autoimmune and inflammatory vascular disorders to prevent thrombotic complications. The mechanism of action of i.v.Ig is, however, not yet elucidated. In view of this, we investigated the ability of i.v.Ig to modulate i) Ca²⁺ signals of fura-2 loaded endothelial cells, and ii) the associated release of nitric oxide (NO) and von Willebrand factor (vWf). NO was measured either indirectly by radioimmunoassay of cGMP in unstimulated cells or directly by electrochemistry at the surface of stimulated endothelial cells from human umbilical cord veins (HUVEC). Short-term treatment of unstimulated HUVEC with intact i.v.Ig decreased the basal cytosolic Ca²⁺ concentration by 20% while it activated the NO/cGMP synthesis. Following i.v.Ig treatment of HUVEC, the Ca²⁺ liberation from internal stores and the vWf secretion induced by ATP, thrombin or histamine were significantly reduced by 38 and 60%, respectively. The effects on Ca²⁺ signals were observed with intact i.v.Ig as well as with the F(ab')₂ or the Fc fragments indicating that both portions are involved in the mechanism of action. The i.v.Ig treatment of HUVECs had no effect on the NO release induced by thrombin or histamine. By contrast, the i.v.Ig treatment increased the ATP-activated NO release by amplifying the Ser1177-eNOS phosphorylation. The i.v.Ig also activated the NO-dependent cGMP release in resting and collagen-stimulated platelets. Since NO is a potent inhibitor of platelet activation and vWF is a platelet adhesion cofactor, the beneficial effects of therapeutic i.v.Ig may lie in the inhibition of platelet adhesion to damaged endothelium.

EL MAHMOUD R., LE FEUVRE C., SANG K.H.L., HELFT G., BEYGUI F., BATISSE J.P., METZGER J.P.

Absence of nephro-protective effect of acetylcysteine in patients with chronic renal failure

investigated by coronary angiography.

Arch. Mal. Coeur Vaisseaux, 96 (12), 1157-1161, 2003

(Services cités : URC)

Recent studies have suggested that an oral dose of acetylcysteine could play a prophylactic role in the prevention of nephrotoxicity from iodine contrast media in patients affected by chronic renal failure. Between June 2001 and September 2002 we selected 120 patients with a basal plasma creatinine level greater than 1.36 mg/dl investigated by coronary angiography. The treatment group included 60 patients who received 600 mg of acetylcysteine in the morning and evening before the day of the examination together with intravenous saline hydration. The control group patients received hydration alone. The clinical characteristics of the groups were comparable as well as the basal plasma creatinine level: 2.01 +/- 1.1 mg/dl in the acetylcysteine group and 1.81 +/- 0.69 in the control group. The plasma creatinine level was measured 24 and 48 hours after coronary angiography. The respective changes in plasma creatinine level at 24 and 48 hours were 0.12 +/- 0.29 and 0.02 +/- 0.29 mg/dl in the acetylcysteine group and 0.06 +/- 0.29 and 0.07 +/- 0.43 mg/dl in the control group (NS). Acute renal failure caused by the contrast medium, defined by an increase of 25% in the plasma creatinine level compared to the basal value, occurred in 3 patients from the acetylcysteine group and 2 patients from the control group. The only predictive factor for acute renal failure was the quantity of contrast medium (316 +/- 141 vs 173 +/- 115 ml, p<0.05). In conclusion, acute renal failure caused by contrast medium is rare in sufficiently hydrated patients with moderate chronic renal failure when a low dose of contrast medium is used. Our study does not confirm a prophylactic effect of acetylcysteine in the prevention of nephrotoxicity from contrast media following coronary angiography in patients with moderate chronic renal failure.

LE GAL G., GOURLET V., HOGREL P., PLU-BUREAU G., TOUBOUL P.J., SCARABIN P.Y.

Hormone replacement therapy use is associated with a lower occurrence of carotid atherosclerotic plaques but not with intima-media thickness progression among postmenopausal women. The vascular aging (EVA) study.

Atherosclerosis, 166 (1), 163-170, 2003

(Services cités : URC)

BACKGROUND: Information on the impact of hormone replacement therapy (HRT) on carotid atherosclerosis is limited. Moreover, transdermal estrogens have not been investigated.

METHODS: We examined association of HRT use with ultrasonographically assessed carotid atherosclerotic plaque occurrence and mean common carotid artery intima-media thickness (CCA-IMT) progression. Within the Vascular Aging (EVA) Study, a community-based cohort, 815 postmenopausal women aged 59-71 have been followed during 4 years. Among these women, 166 had already used HRT. **RESULTS:** Women who had ever used HRT experienced a lower occurrence of plaques (8.6 versus 19.1%, P=0.003). After adjustment for the main cardiovascular risk factors, odds-ratio for plaque occurrence was 0.41 (95% confidence interval 0.21-0.78, P=0.01) among ever users of HRT compared with never users. When transdermal route of estrogen administration was used, adjusted odds-ratio was 0.66 (95% confidence interval 0.47-0.99, P=0.04). The progression of IMT, which was measured at a plaque-free site and adjusted on initial levels of CCA-IMT did not differ between ever and never users of HRT. It was 0.011 mm per year among ever users and 0.012 mm per year among never users (P=0.61).

CONCLUSION: These data suggest that HRT use may prevent the development of atherosclerotic plaques in postmenopausal women, especially when estrogens are administered by

transdermal route.

SAMAMA M.M., RACHED R.A., HORELLOU M.H., AQUILANTI S., MATHIEUX V.G., PLU-BUREAU G., ELALAMY I., CONARD J.

Pregnancy-associated venous thromboembolism (VTE) in combined heterozygous factor V Leiden (FVL) and prothrombin (FII) 20210 A mutation and in heterozygous FII single gene mutation alone.

Br. J. Haematol., 123 (2), 327-334, 2003

(Services cités : URC)

The risk of venous thromboembolism (VTE) in the absence of prophylaxis was evaluated in a retrospective study of 47 women (84 pregnancies) with combined thrombophilia [heterozygous factor V Leiden (FVL) plus prothrombin (FII) 20210A mutation (group I)] and in 82 women (193 pregnancies) with the FII alone (group II). VTE was more frequent in group I than in group II [17.8% versus 6.2%, $P = 0.003$, relative risk (RR) 2.9, 95% confidence interval (CI) 1.4-5.9], ante partum (7.1% and 2.1%) and post partum (11.5% and 4.2%). The risk was higher in index cases than in family members (RR 2.5, 95% CI 1.2-5.2 and RR 2.1, 95% CI 0.2-22.3 respectively) Even women who had no history of VTE before pregnancy had an increased risk (RR 2.2, 95% CI 1.0-4.8). Our results suggest that, during ante partum, prophylaxis is indicated in women with combined thrombophilia and with a VTE before pregnancy. In those without VTE before pregnancy, prophylaxis might be decided for each individual case, taking into consideration all risk factors. In women with the FII mutation alone, the low risk may not justify prophylaxis in the absence of previous VTE. In post partum, prophylaxis is indicated in all cases.

SCARABIN P.Y., OGER E., PLU-BUREAU G.

Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk.

Lancet, 362 (9382), 428-432, 2003

(Services cités : URC)

BACKGROUND: Oral oestrogen-replacement therapy (ERT) activates blood coagulation and increases the risk of venous thromboembolism (VTE) in postmenopausal women. Transdermal ERT has little effect on haemostasis, but data assessing its effect on thrombotic process are scarce. We aimed to examine the effect of the route of oestrogen administration on VTE risk. **METHODS:** We did a multicentre hospital-based case-control study of postmenopausal women in France. During 1999-2002, we recruited 155 consecutive cases with a first documented episode of idiopathic VTE (92 with pulmonary embolisms and 63 with deep venous thrombosis), and 381 controls matched for centre, age, and time of recruitment. **FINDINGS:** Overall, 32 (21%) cases and 27 (7%) controls were current users of oral ERT, whereas 30 (19%) cases and 93 (24%) controls were current users of transdermal ERT. After adjustment for potential confounding variables, the odds ratio for VTE in current users of oral and transdermal ERT compared with non-users was 3.5 (95% CI 1.8-6.8) and 0.9 (0.5-1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (1.9-8.3). **INTERPRETATION:** Oral but not transdermal ERT is associated with risk of VTE in postmenopausal women. These data suggest that transdermal ERT might be safer than oral ERT with respect to thrombotic risk.

2002

CLEMENT F., MONNIAUX D., THALABARD J.C., CLAUDE D.

Contribution of a mathematical modelling approach to the understanding of the ovarian function. *C. R. Biol.*, 325 (4), 473-485, 2002

(Services cités : Biostatistique, Endocrinologie & Médecine de la Reproduction, URC)

The biological meaning of folliculogenesis is to free fertilisable oocytes at the time of ovulation. We approached the study of the control of follicular development at the level of follicular granulosa cells, on the experimental as well as mathematical modelling grounds. We built a mathematical model allowing for the processes of proliferation, differentiation and apoptosis. State variables correspond to the numbers of cells undergoing these different processes, while control variables correspond to the cellular transition rates. The model results raised the notion of proliferative resources, which leads to consider the optimal management of these resources and has motivated the settling of an experiment investigating the changes in the growth fraction within the granulosa throughout terminal development. We are now investigating the way gonadotrophins, and especially FSH, operate on granulosa cells, in order to account for the hormonal control of the divergent commitment of granulosa cells towards either proliferation, differentiation or apoptosis. We are thus focusing on the dynamics of cAMP production, which appears to be a keypoint in FSH signal transduction. (C) 2002 Academie des sciences/Editions scientifiques et medicales Elsevier SAS.

MAHIEU-CAPUTO D., MULLER F., JOUVET P., THALABARD J.C., JOUANNIC J.M., NIHOUL-FEKETE C., DUMEZ Y., DOMMERGUES M.

Amniotic fluid beta-endorphin: A prognostic marker for gastroschisis ?

J. Pediat. Surg., 37 (11), 1602-1606, 2002

(Services cités : Chirurgie Pédiatrique, Endocrinologie & Médecine de la Reproduction, Maternité, Biostatistique, URC)

PURPOSE: The aim of this work was to study amniotic fluid beta-endorphin as a potential predictor for postnatal morbidity in gastroschisis. **METHODS:** Beta-endorphin was assayed in 43 amniotic fluid samples from 13 pregnant women with fetal gastroschisis undergoing diagnostic amniocentesis or therapeutic amnioinfusion and compared with 33 controls. Within the gastroschisis group, the authors investigated the relationship between postnatal morbidity and the peak value of amniotic fluid beta-endorphin (AFBE). **RESULTS:** Ten AFBE values in 6 cases of gastroschisis were above the upper limit of the 95% confidence interval derived from controls. Postnatal morbidity was significantly higher when peak AFBE exceeded 10 $\mu\text{g/L}$ (n = 4 pregnancies) compared with below 5 $\mu\text{g/L}$ (n = 9 pregnancies), as shown by mean duration of mechanical ventilation (15.2 v 3 days; P =.01), of parenteral feeding (77 v. 18.7 days; P =.04), and of hospitalization (84 v 32.2 days; P =.04). There was no statistically significant association between postnatal morbidity markers and prenatal dilation of fetal bowel. **CONCLUSIONS:** The most severe cases of gastroschisis are associated with high levels of AFBE. The authors speculate that this fetal hormonal response could result from stress or pain caused by prenatal bowel damage. *J Pediatr Surg* 37:1602-1606. Copyright 2002, Elsevier Science (USA). All rights reserved.

MULLER F., THALABARD J.C., NGO S., DOMMERGUES M.

Detection and false-positive rates of maternal serum markers for Down syndrome screening according to maternal age in women over 35 years of age. A study of the agreement of eight dedicated software packages.

Prenat. Diag., 22 (5), 350-353, 2002

(Services cités : Endocrinologie & Médecine de la Reproduction, Maternité, URC)

Maternal serum markers for trisomy 21 screening (MSS) can be assayed in women ≥ 35 years in an attempt to reduce the need for invasive procedures and thereby avoid their side effects. Our objective was to compare, in women ≥ 35 , eight different software packages dedicated to second trimester MSS, thus providing reliable data for patient counselling. A simulation study was carried out on 189 sera from women with Down syndrome fetuses and 11 962 sera from mothers of unaffected babies. The first step was to estimate the joint distribution of alpha-fetoprotein (AFP) and free beta-human chorionic gonadotrophin (beta-hCG). The second step was to calculate trisomy 21 detection and false-positive rates for each software according to maternal age (35-45 years), using the usual 1:250 risk threshold. Agreement between software packages was measured using 2x2 kappa coefficients. Detection rates and false-positive rates increased with maternal age. Depending on the software, 57-71% detection rates were achieved at 35 years with 12-18% false-positive rates. At 45 years, 61-100% detection rates were achieved with 66-95% false-positive rates. Up to 39 years, all softwares were concordant (kappa coefficients > 0.75). In the range 35-45 years, false-positive and detection rates increased substantially with maternal age and differences between software packages are observed.

VAYSSIERE C., MORINIERE C., CAMUS E., LE STRAT Y., POTY L., FERMANIAN J., VILLE Y.

Measuring cervical length with ultrasound: evaluation of the procedures and duration of a learning method.

Ultrasound Obstet. Gynecol., 20 (6), 575-579, 2002

(Services cités : Biostatistique, URC)

OBJECTIVE: To evaluate the learning curve and principal learning steps for a novice ultrasound operator to master the technique for measuring cervical length by transvaginal ultrasound.

SUBJECTS AND METHODS: The study involved asymptomatic patients with a singleton pregnancy between 21 and 38 weeks attending for a routine ultrasound scan. Two operators new to cervical ultrasound including one with experience in transvaginal gynecological ultrasound were assessed during their training. After an initial lecture session on the technique of cervical measurement, the trainees had one or two supervised practice sessions, validated by two interobserver agreement studies with 30 patients at a time; these compared the level of agreement between trainer and trainee throughout. Five examinations were performed in the first practice session; a second session was planned if the trainee could not perform all five examinations alone satisfactorily, in agreement with four quality criteria predefined for good cervical measurements. The second session lasted until five consecutive examinations could be performed adequately without the trainer's aid. Agreement between the two operators was assessed by intraclass correlation coefficient (ICC). The ICCs were compared with Fisher's Z transformation.

RESULTS: Of the 150 patients included, 2.7% gave birth before term. The trainee with no experience in transvaginal ultrasound required two practice sessions; none of the five ultrasound scans performed in the first session was correct. In the second session, 18 consecutive ultrasound examinations were necessary to obtain five consecutive adequate results. During interobserver studies with the trainer, the ICC progressed from 0.43 in the first study to 0.64 in the second and 0.77 in the third ($P = 0.049$ between the first and third studies). The trainee with experience in transvaginal ultrasound required only one practice session. The ICC increased from 0.73 to 0.85 in the two interobserver studies with the trainer. **CONCLUSIONS:** Measurement of cervical length by transvaginal ultrasound examination is a technique that can be learnt rapidly. While roughly 23 supervised ultrasound scans appear necessary for an operator with no experience in transvaginal ultrasound, substantially fewer are required for an operator already familiar with this

approach for other indications.

2001

AUDIBERT F., DOMMERGUES M., BENATTAR C., TAIEB J., THALABARD J.C., FRYDMAN R.

Screening for down syndrome using first-trimester ultrasound and second-trimester maternal serum markers in a low-risk population: a prospective longitudinal study.

Ultrasound Obstet. Gynecol., 18 (1), 26-31, 2001

(Services cités : Biostatistique, Endocrinologie & Médecine de la Reproduction, URC)

Objectives To compare nuchal translucency and second-trimester maternal serum measurements as alternative methods of antenatal screening for Down syndrome in a low-risk population and to evaluate the consequence of combining the results in the estimation of risk. Design In a consecutive series of 4130 women aged less than 38 years with a singleton pregnancy, we examined both the detection rate of Down syndrome by nuchal translucency measurement at 10-14 weeks and maternal serum screening by human chorionic gonadotrophin and alpha-fetoprotein at 14-18 weeks. Women with a nuchal translucency, measurement of greater than or equal to 3 mm and women with a maternal serum screening-derived risk greater than or equal to 1/250 were recommended to have amniocentesis. A second-trimester detailed ultrasound scan was also performed in all women. The outcome of all pregnancies was recorded prospectively and the detection rate and false-positive rate of different screening strategies were retrospectively analyzed. Results Out of the 4130 pregnancies that were followed (mean maternal age, 30.1 years), 12 cases of Down syndrome were observed (0.28%), all detected prenatally. Seven of 12 cases had a nuchal translucency measurement of greater than or equal to 3 mm (58%), and six out of 10 cases with available maternal serum screening had a calculated risk of greater than or equal to 1/250 (60%). Four of the five Down syndrome cases with a nuchal translucency measurement of < 3 mm were detected by subsequent maternal serum screening. At a threshold giving 5% of positive tests, the sensitivity of nuchal translucency, maternal serum screening and combined risk screening were 75%, 60% and 90%, respectively. Conclusions In screening for Down syndrome, an approach which combines the results from first-trimester nuchal translucency and second-trimester biochemistry, is effective and increases the detection rate compared to the use of any single test. However, this strategy is likely to raise the false-positive rate and the interpretation of maternal serum screening-derived risk should be combined with the first-trimester nuchal translucency measurement. [References: 23]

CLEMENT F., MONNIAUX D., STARK J., HARDY K., THALABARD J.C., FRANKS S., CLAUDE D.

Mathematical model of fsh-induced camp production in ovarian follicles.

Amer. J. Physiol. - Endocrinol. Met., 281 (1), E35-E53, 2001

(Services cités : Biostatistique, URC)

During the terminal part of their development, ovarian follicles become totally dependent on gonadotropin supply to pursue their growth and maturation. Both gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), operate mainly through stimulatory G protein-coupled receptors, their signal being transduced by the activation of the enzyme adenylyl cyclase and the production of second-messenger cAMP. In this paper, we develop a mathematical model of the dynamics of the coupling between FSH receptor stimulation and cAMP synthesis. This model takes the form of a set of nonlinear, ordinary differential equations that describe the changes in the different states of FSH receptors (free, bound, phosphorylated, and internalized),

coupling efficiency (activated adenylyl cyclase), and cAMP response. Classical analysis shows that, in the case of constant FSH signal input, the system converges to a unique, stable equilibrium state, whose properties are here investigated. The system also appears to be robust to nonconstant input. Particular attention is given to the influence of biologically relevant parameters on cAMP dynamics. [References: 38]

**MAHIEU-CAPUTO D., SONIGO P., DOMMERGUES M., FOURNET J.C.,
THALABARD J.C., ABARCA C., BENACHI A., BRUNELLE F., DUMEZ Y.**

Fetal lung volume measurement by magnetic resonance imaging in congenital diaphragmatic hernia.

Br. J. Obstet. Gynaecol., 108 (8), 863-868, 2001

(Services cités : Maternité, Radiologie Pédiatrique, URC)

Objective To study the potential for prenatal magnetic resonance imaging to predict pulmonary hypoplasia in congenital diaphragmatic hernia. Design Prospective observational study. Setting Tertiary care centre. Participants Thirteen cases of congenital diaphragmatic hernia (11 left, 2 right) without associated anomalies and 74 controls. Methods Measurements by magnetic resonance imaging of fetal lung volume were achieved. In the control fetuses, a regression analysis was performed to associate fetal lung volume with gestational age. This yielded a formula allowing calculation of the expected fetal lung volume as a function of gestational age. In the cases with congenital diaphragmatic hernia, the observed/expected fetal lung volume ratio was compared with perinatal outcome. Main outcome measures Neonatal mortality and pulmonary hypoplasia, which was defined as lung/body weight ratios less than 0.012. C, Results The expected fetal lung volume was derived from the following formula: Fetal lung volume (mL) $\exp(1.24722 + 0.08939 \times \text{gestational age in weeks})$. The observed/expected fetal lung volume ratio was significantly lower in congenital diaphragmatic hernia (median: 0.31, range: 0.06-0.63), than in controls (median: 0.99, range: 0.42-1.94). This ratio was significantly less in the infants with congenital diaphragmatic hernia who died (median: 0.26, range: 0.06-0.63) compared with those who survived (median: 0.46, range: 0.35-0.56). The observed: expected fetal lung volume ratio was significantly correlated with the postmortem lung: body weight ratio. Conclusion In isolated con-enital diaphragmatic hernia, fetal lung volume measurement by magnetic resonance C imaging is a potential predictor of pulmonary hypoplasia and postnatal outcome. Further studies are required C, to establish the clinical value of macynetic resonance imaging for the prenatal assessment of fetal lungs. [References: 25]

MARQUE V., ALHENC-GELAS M., PLU-BUREAU G., OGER E., SCARABIN P.Y.

The effects of transdermal and oral estrogen/progesterone regimens on free and total protein S in postmenopausal women.

Thromb. Haemost., 86 (2), 713-714, 2001

(Services cités : URC)

**OGER E., ALHENC-GELAS M., PLU-BUREAU G., MENNEN L., CABBILLAU M.,
GUIZE L., PUJOL Y., SCARABIN P.**

Association of circulating cellular adhesion molecules with menopausal status and hormone replacement therapy. Time-dependent change in transdermal, but not oral estrogen users.

Thromb. Res., 101 (2), 35-43, 2001

(Services cités : URC)

The incidence of coronary heart disease is lower in premenopausal than in postmenopausal

women, and estrogen use may be cardioprotective among postmenopausal women. Cellular adhesion molecules (CAM) are involved in the early stage of atherosclerosis, and short-term administration of oral estrogen decreased plasma concentrations of their soluble forms in postmenopausal women. However, data evaluating transdermal estrogen are sparse and long-term effect of hormone replacement therapy (HRT) on CAM is unknown. Therefore, we have investigated the association of circulating CAM (cCAM) with menopausal status and long-term HRT. Plasma levels of intercellular adhesion molecule-1 (cICAM-1), vascular cell adhesion molecule-1 (cVCAM-1), P-selectin, E-selectin, C-reactive protein (CRP), and fibrinogen were measured in 74 premenopausal women, 60 postmenopausal women not using HRT, 30 postmenopausal women using opposed oral estrogen therapy, and 30 postmenopausal women using opposed transdermal estrogen therapy. All women were apparently healthy and aged between 45 and 54 years. Duration of HRT ranged from 3 to 96 months. Postmenopausal women not receiving HRT had 24% higher mean levels of cICAM-1 than premenopausal women (318 vs. 255 ng/ml, $P < .001$). In postmenopausal women, users of oral estrogen had 16% lower, and users of transdermal estrogen had 17% lower mean levels of cICAM-1 than non-users (268 and 264 vs. 318 ng/ml, $P = .001$ for both comparisons). Furthermore, in users of transdermal route, the lowering effect of estrogen on cICAM-1 was dependent on treatment duration, while no time-dependent effect was seen in oral estrogen users. Users of transdermal estrogen had lower cVCAM-1 and P-selectin levels than postmenopausal non-users (327 vs. 364 ng/ml ($P = .05$) and 18 vs. 23 ng/ml ($P = .05$). There was no difference in CRP and E-selectin levels between the groups. Adjustment for age and body mass index (BMI) made no substantial change in the results. These data suggest that oral and transdermal estrogen may play a long-term cardioprotective role through favourable changes in endothelial function.

TOURAINÉ F., PLU-BUREAU G., BEJI C., MAUVAIS-JARVIS F., KUTTENN F.

Long-term follow-up of 246 hyperprolactinemic patients.

Acta Obstet. Gynecol. Scand., 80 (2), 162-168, 2001

(Services cités : Endocrinologie & Médecine de la Reproduction, U344, URC)

Background. We wanted to evaluate the very long-term effects of bromocriptine on prolactin (PRL) levels and pituitary tumor size in a large cohort of hyperprolactinemic patients. Methods. We conducted a retrospective cohort study in the Department of Endocrinology from Necker Hospital in Paris, France. Two hundred and forty-six patients consulted primarily for menstrual disorders, with diagnosis of hyperprolactinemia. Patients were followed-up for 99.9+/-3.6 months. One hundred and ninety-one were treated with bromocriptine, 32 underwent surgery, and 23 received no treatment. Results. The mean initial plasma PRL level was 135.0+/-20.2 ng/ml. Presence of an adenoma was detected in 60% of our patients and comprised a microadenoma in 64% of cases. Compared to oligomenorrheic women, amenorrheic patients had significantly higher levels of PRL and larger pituitary tumor size. In the bromocriptine group, PRL levels decreased from 99.6+/-7.9 to 20.0+/-1.5 ng/ml ($p=0.00001$). The medical treatment was associated with disappearance of the adenoma in 45% of the women and with stabilization of pituitary tumor size in 40% of patients. Surgery led to disappearance of the adenoma in almost all cases, but failed to definitively cure hyperprolactinemia. Conclusion. In this large-scale retrospective study, the medical treatment of mild hyperprolactinemia was shown to be effective and sufficient after 9 years of follow-up. [References: 43]

TOURAINÉ P., PLU-BUREAU G., BERESSI N., DECQ P., THALABARD J.C., KUTTENN F.

Resumption of luteinizing hormone pulsatility and hypogonadotropic hypogonadism after endoscopic ventriculocisternostomy in a hydrocephalic patient.

Fert. Steril., 76 (2), 390-393, 2001

(Services cités : Endocrinologie & Médecine de la Reproduction, U344, URC)

OBJECTIVE: To study gonadotropin pulsatility before and after surgical cure of hydrocephalus.

DESIGN: Case report. SETTING: Department of Endocrinology and Centre d'Investigations

Cliniques, Necker Hospital, Paris, France. PATIENT(S): A 29-year-old woman who presented with secondary amenorrhea. INTERVENTION(S): The patient underwent an endoscopic

ventriculocisternostomy that led to restoration of normal menses and resolution of

hypogonadism. MAIN OUTCOME MEASURE(S): A gonadotropin pulse study was performed

before and 2 and 5 months after surgery. RESULT(S): No LH pulse was observed before surgery.

Emergence of pulsatility was observed 2 months after surgery, and pulses became clearly

individualized after 5 months. CONCLUSION(S): This observation strongly suggests that amenorrhea, in case of chronic hydrocephalus, is indeed due to a hypothalamic dysfunction of the GnRH pulse generator.

2000

BERNIER M.O., PLU BUREAU G., BOSSARD N., AYZAC L., THALABARD J.C.

Breastfeeding and risk of breast cancer: a metaanalysis of published studies.

Hum. Reprod. Update, 6 (4), 374-386, 2000

(Services cités : Endocrinologie & Médecine de la Reproduction, Biostatistique, URC)

Evidence in favour of an association of breastfeeding with a breast cancer risk reduction remains

limited and inconsistent. To evaluate the relation between breastfeeding and breast cancer, a

meta-analysis based on a review of the literature was carried out, using as variables ever/never

breastfeeding and duration of breastfeeding, Menopausal status at the time of diagnosis of breast

cancer was considered to be a potential effect modifier, Only case-control studies could be

included in the final analysis. A slight but significant decreased risk of breast cancer was

observed in ever breastfeeding, compared with never breastfeeding parous women, using both the

fixed and random-effect models. This decrease was more pronounced in non-menopausal women

at the time of diagnosis of breast cancer and in long-term breastfeeding women. Hence,

breastfeeding appeared to be a protective factor but was of small magnitude compared with other

known risk factors for breast cancer. Whether this result should imply a modification in the

attitude of both health care providers and women towards breastfeeding, which represents one of

the few identified protective factors which is under the control of the mother, and is thus

(theoretically) modifiable, remains questionable. [References: 84]

LE QUAN SANG K.H., LE FEUVRE C., BRUNET A., PHAM T.D., METZGER J.P., VACHERON A., DEVYNCK M.A.

Influence of sin-1 on platelet ca²⁺ handling in patients with suspected coronary artery disease: ex vivo and in vitro studies.

Thromb. Haemost., 83 (5), 752-758, 2000

(Services cités : UMR 8604, Cardiologie Adulte, URC)

The 3-morpholinoydnonimine (SIN-1) generates both nitric oxide (NO) and superoxide anion

(O²⁻). It elicits dose-dependent vasodilation in vivo, in spite of the opposite effects of its

breakdown products on vascular tone and platelet aggregation. This study was designed to

investigate the influence of intravenous SIN-1 injection on platelet Ca²⁺ handling in patients

undergoing coronary angiography. SIN-1 administration reduced cytosolic [Ca²⁺] in

unstimulated platelets by decreasing Ca²⁺ influx. It attenuated Ca²⁺ mobilization from internal stores evoked by thrombin or thapsigargin. In vitro studies were used as an approach to investigate how simultaneous productions of NO and O₂⁻ from SIN-1 modify thrombin- or thapsigargin-induced platelet Ca²⁺ mobilization. Superoxide dismutase, the O₂⁻ scavenger, enhanced the capacity of SIN-1 to inhibit Ca²⁺ mobilization but catalase had no effect. This suggests that the effects of SIN-1 on platelet Ca²⁺ handling resemble those of NO, but are modulated by simultaneous O₂⁻ release, independently of H₂O₂ formation. [References: 50]

LE STRAT Y., THOMAS G., THALABARD J.C.

A Markov regression model for the analysis of the postpartum lactational amenorrhea.

Commun. Stat.-Stimul. Computa., 29 (.), 1125, 2000

(Services cités : URC)

OGER E., ALHENC-GELAS M., PLU-BUREAU G., GUIZE L., SCARABIN P.Y.

Plasma 17beta estradiol is inversely correlated with circulating vascular cell adhesion molecule.

Thromb. Haemost., 84 (6), 1125, 2000

(Services cités : URC)

PLU BUREAU G., BOSSARD N., THALABARD J.C.

Oral contraception and genetic factors in breast cancer: characteristics and limits of case-only studies.

Rev. Épidémiol. Santé Publ., 48 (3), 294-303, 2000

(Services cités : Endocrinologie & Médecine de la Reproduction, URC)

The analysis of the interaction between environmental and genetic factors is a matter of increasing interest in cancerology. More particularly the discovery of the BRCAx family and the high cumulated incidence of familial breast cancers related to mutations of these proteins raised the issue of the differential effect of long term and/or early exposure to oral contraceptives in the presence of these mutations. The classical case-control design assumes the presence of a control group, which can be sometimes difficult to obtain from both the technical and ethical points of view. Case-only or case-case studies, which are based only on series of cases, making them apparently attractive, have been proposed to analyze more specifically the interaction term. The aim of the present paper is to review and discuss the methodological basis and main assumptions of the case-only design, and their applicability to breast cancer studies. The measure of the interaction between an environmental factor and a susceptibility genetic factor differs in an important aspect from the measure of the association between an environmental factor and acquired tumoral genetic factor; this aspect is reminded. [References: 27]