Cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer (CIRCCa): a randomised, double-blind, placebo-controlled phase 2 trial.

Patients treated with standard chemotherapy for metastatic or relapsed cervical cancer respond poorly to conventional chemotherapy with an overall survival of less than 1 year. High tumour angiogenesis and high concentrations of intratumoural VEGF are adverse prognostic features. Cediranib is a potent tyrosine kinase inhibitor of VEGFR1, 2, and 3.

The effect of the addition of cediranib to carboplatin and paclitaxel chemotherapy in patients with metastatic or recurrent cervical cancer was assessed. A randomised, double-blind, placebo-controlled phase 2 trial, was done in 17 UK cancer treatment centres. Patients aged 18 years or older initially diagnosed with metastatic carcinoma or who subsequently developed metastatic disease or local pelvic recurrence after radical treatment that was not amenable to exenterative surgery were recruited. Eligible patients received carboplatin plus paclitaxel by infusion every 3 weeks for a maximum of six cycles and were randomised centrally (1:1) through a minimisation approach to receive cediranib 20 mg or placebo orally once daily until disease progression. The primary endpoint was progression-free survival. Efficacy analysis was by intention to treat, and the safety analysis included all patients who received at least one dose of study drug.

Between 19.8.2010, and 27.7.2012, 69 patients were enrolled and randomly assigned to cediranib (n=34) or placebo (n=35). After a median follow-up of 24-2 months, progression-free survival was longer in the cediranib group (median 8-1 months [80% CI 7.4–8-8]) than in the placebo group (6-7 months), with a hazard ratio (HR) of 0-58 (80% CI 0.40–0.85; one-sided p=0.032).

Grade 3 or worse adverse events that occurred in the concurrent chemotherapy and trial drug period in more than 10% of patients were diarrhoea (16% in the cediranib group vs 3% in the placebo group), fatigue (13% vs 6%), leucopenia (16% vs 9%), neutropenia (31% vs 11%), and febrile neutropenia (16% vs none). The incidence of grade 2–3 hypertension was higher in the cediranib group than in the control group (34% vs 11%). Serious adverse events occurred in 18 patients in the placebo group and 19 patients in the cediranib group.

Cediranib has significant efficacy when added to carboplatin and paclitaxel in the treatment of metastatic or recurrent cervical cancer. This finding was accompanied by an increase in toxic effects (mainly diarrhoea, hypertension, and febrile neutropenia).


Measurement and validation of frailty as a predictor of outcomes in women undergoing major gynaecological surgery

Frailty is the loss of physical or mental reserve that impairs function, often in the absence of a defined comorbidity. A retrospective cohort study was done among the hospitals across the USA participating in the National Surgical Quality Improvement Program (NSQIP) from 2008 to 2012 to determine whether a modified frailty index (mFI) correlates with morbidity and mortality in patients undergoing hysterectomy.

An mFI was calculated using 11 variables in NSQIP. The associations between mFI and morbidity and mortality were assessed. Model fit statistics (c-statistics) were utilised to evaluate the ability of mFI to distinguish outcomes like wound infection, severe complications and mortality.

A total of 66 105 patients were identified. Wound complications increased from 2.4% in patients with an mFI of zero to 4.8% in those with mFI e”0.5 (P < 0.0001). Similarly, severe complications increased from 0.98% to 7.3% (P < 0.0001), overall complications rose from 3.7% to 14.5% (P < 0.0001) and mortality increased from 0.06% to 3.2% (P < 0.0001) for patients with a frailty index of zero.
compared with those with an index of e\(^0.5\). Versus chance, the goodness-of-fit c-statistics suggested that mFI increases the ability to detect wound complications by 11.4%, severe complications by 22.0% and overall complications by 11.0%.

The mFI is easily reproducible from routinely collected clinical data and predictive of outcomes in patients undergoing hysterectomy. Frailty may be useful in the preoperative risk assessment of women undergoing gynaecological surgery.


**Does oral carbohydrate supplementation improve labour outcome? A systematic review and individual patient data meta-analysis.**

Labour is a period of significant physical activity. The importance of carbohydrate intake to improve outcome has been recognised in sports medicine and general surgery. Study has been done to assess the effect of oral carbohydrate supplementation on labour outcomes.

In randomised controlled trials (RCT), women were randomised to receive oral carbohydrate in labour (<6 cm dilated), versus placebo or standard care. Individual patient data meta-analyses were performed to calculate pooled risk ratios (RR) and 95% confidence intervals (CI).

Eight RCTs met the inclusion criteria. Six authors responded, four supplied data (n = 691). Three studies used isotonic drinks (one placebo-controlled, two compared with standard care), and one an advice booklet regarding carbohydrate intake. The mean difference in energy intake between the intervention and control groups was small [three studies, 195 kilocalories (kcal), 95% CI 118–273]. There was no difference in the risk of caesarean section (RR 1.15, 95% CI 0.83–1.61), instrumental birth (RR 1.26, 95% CI 0.96–1.66) or syntocinon augmentation (RR 0.99, 95% CI 0.86–1.13). Length of labour was similar (mean difference ~3.15 minutes, 95% CI 35.14 to 41.95). Restricting the analysis to primigravid women did not affect the result.

Oral carbohydrates did not increase the risk of vomiting (RR 1.09, 95% CI 0.78–1.52) or 1-minute Apgar score <7 (RR 1.23, 95% CI 0.82–1.83).

Conclusion, Oral carbohydrate supplements in small quantities did not alter labour outcome.


**Antenatal care for healthy pregnant women: a mapping of interventions from existing guidelines to inform the development of new WHO guidance on antenatal care**

The World Health Organization (WHO) is in the process of updating antenatal care (ANC) guidelines. To map the existing clinical practice guidelines related to routine ANC for healthy women and to summarise all practices considered during routine ANC, a systematic search in four databases for all clinical practice guidelines published after January 2000.

Information on scope of the guideline, type of practice, associated gestational age, recommendation type and the source of evidence were mapped.

Of 1866 references, 85 guidelines were identified focusing on the ANC period: 15 pertaining to routine ANC and 70 pertaining to specific situations. A total of 135 interventions from routine ANC guidelines were extracted, and categorized as clinical interventions (n = 80), screening/diagnostic procedures (n = 47) and health systems related (n = 8). Screening interventions, (syphilis, anaemia) were the most common practices. Within the 70 specific situation guidelines, 102 recommendations were identified. Overall, for 33 (out of 171) interventions there were conflicting recommendations provided by the different guidelines.

Mapping the current guidelines including practices related to routine ANC informed the scoping phase for the WHO guideline for ANC. The analysis indicates that guideline development processes may lead to different recommendations, due to context, evidence base or assessment of evidence. It would be useful for guideline developers to map and refer to other similar guidelines and, where relevant, explore the discrepancies in recommendations and others.
Abstracts


**The effects of single-dose dexamethasone on inflammatory response and pain after uterine artery embolisation for symptomatic fibroids or adenomyosis: a randomised controlled study**

A prospective, randomised, double-blind, and placebo-controlled study was done in a tertiary-care University centre in Korea. The study investigated the effects of single-dose intravenous dexamethasone on inflammatory responses, pain, nausea, and vomiting after uterine artery embolisation (UAE) in patients undergoing the procedure for the treatment of symptomatic fibroids or adenomyosis. Sixty-four patients were enrolled and 59 patients completed the study. They were randomised to receive either intravenous dexamethasone (10 mg; dexamethasone group) or normal saline (control group) 1 hour before UAE. Both groups received fentanyl-based intravenous patient-controlled analgesia (PCA) during the 24 hours after UAE.

The primary outcomes were the inflammatory and stress responses measured by white blood cell count, neutrophil percentage, C–reactive protein (CRP), interleukin–6 (IL–6), and cortisol. Secondary outcomes were severity of pain and incidence of nausea and vomiting.

CRP, IL–6, and cortisol were significantly lower in the dexamethasone group compared with the control group after 24 hours after UAE. Although the cumulative dose of fentanyl and additional analgesics administered during the 24 hours after UAE were similar between the two groups, pain scores were significantly lower in the dexamethasone group from 12 hours after UAE, and the incidence of severe nausea and vomiting was lower in the dexamethasone group.

Conclusion: The administration of single-dose intravenous dexamethasone as an adjunct to fentanyl-based intravenous PCA is effective in reducing inflammation and pain during the first 24 hours after UAE.


**Invasive therapies for primary postpartum haemorrhage: a population-based study in France**

A population-based observational study was carried on among 146781 women delivering between 2004 and 2006 in 106 maternity units of six French regions. The study described the characteristics, management, and outcomes of women undergoing invasive therapies for primary postpartum haemorrhage (PPH).

Prospective identification of women with PPH managed with invasive therapies, including uterine suture, pelvic vessel ligation, arterial embolisation, and hysterectomy.

Main outcome measured the rate of use and failure rate of invasive therapies, with 95% confidence intervals (95% CIs).

An invasive therapy was used in 296 of 6660 women with PPH (4.4%, 95% CI 4.0–5.0), and in 0.2% of deliveries (95% CI 0.18–0.23). A hysterectomy was performed in 72/6660 women with PPH (1.1%, 95% CI 0.8–1.4%), and in 0.05% of deliveries (95% CI 0.04–0.06). A conservative invasive therapy was used in 262 women, including 183 (70%) who underwent arterial embolisation and 79 (30%) who had conservative surgery as the first-line therapy. Embolisation was more frequently used after vaginal than caesarean delivery, and when arterial embolisation was available on site. The failure rate of conservative invasive therapies was 41/262 (15.6%, 95% CI 11.5–20.6) overall, and was higher after surgical than after embolisation procedures, in particular for vaginal deliveries.

Both maternal mortality as a result of obstetric haemorrhage and the rate of invasive therapies used for PPH are high in France. These findings suggest flaws in the initial management of PPH and/or the inadequate use of invasive procedures.