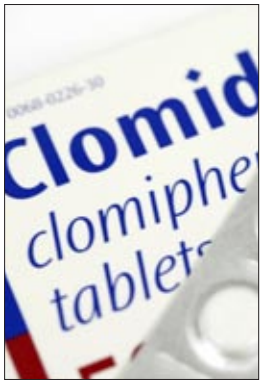
Fertility drugs and ovarian cancer

Current evidence shows no increased risk



CUSTOM MEDICAL STOCK PHOTO/SPL

RESEARCH, p 580

Penelope M Webb senior research fellow, Queensland Institute of Medical Research, Royal Brisbane Hospital, Brisbane, QLD 4029, Australia
Penny.Webb@qimr.edu.au

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:a3075
doi: 10.1136/bmj.a3075

During the past two decades, considerable debate has centred around whether the use of fertility drugs increases a woman's risk of developing ovarian cancer. Most ovarian cancers are assumed to arise from the layer of epithelial cells surrounding the ovary, and it has been suggested that the repeated cycle of damage and repair that occurs with ovulation may lead to DNA damage and potentially cancer—the so called "incessant ovulation" hypothesis.[1] By stimulating hyperovulation, fertility drugs might therefore increase the risk of cancer. A second hypothesis posits that increasing exposure to gonadotrophins increases the risk of ovarian cancer,[2] and because gonadotrophins are used to treat infertility, such treatment might, theoretically, put patients at risk. In the linked study, Jensen and colleagues use data from a large cohort study of infertile women to assess the effects of fertility drugs on the risk of ovarian cancer.[3]

Anxiety was initially fuelled by two studies suggesting that women who had taken fertility drugs had an increased risk of developing ovarian cancer.[4 5] However, these studies included only 20 and 11 women with ovarian cancer who had used fertility drugs. Subsequent studies have generally reported no association,[6] but concerns remain, particularly for women who undergo 12 or more cycles of treatment or who never succeed in becoming pregnant. For example, a Cochrane review on the use of clomifene citrate for unexplained subfertility mentions that use for more than 12 cycles has been associated with increased risk of ovarian cancer.[7] Cochrane reviews are, rightly, highly respected and widely accessible to clinicians and patients, yet the body of the review suggests the statement about ovarian cancer risk is based solely on the results of the early studies.[4 5] So should women seeking treatment for infertility be worried that fertility drugs might increase their risk of ovarian cancer?

More than 10 cohort studies and a similar number of case-control studies have attempted to answer this question. Most have been limited by small sample sizes—only three studies have included more than 25 women with ovarian cancer who have used fertility drugs.[8-10] Furthermore, infertility itself is a risk factor for ovarian cancer,[9] but many studies have been unable to separate the potential effects of the use of fertility drugs on the risk of ovarian cancer from the effects of the underlying infertility; others could not control for potentially important confounding factors such as parity and use of oral contraceptives.

Jensen and colleagues' study included 54 362 women with infertility problems referred to Danish fertility clinics from 1963 to 1998.[3] It found that use of four groups of fertility drugs (gonadotrophins, clomifenes, human chorionic gonadotrophin, and gonadotrophin releasing hormone) was not associated with an overall increase in the risk of ovarian cancer. They also found no suggestion that risk was increased in women who had undergone 10 or more cycles of treatment or in those who remained nulliparous. Although the authors did see a significantly increased risk of the most common serous subtype of ovarian cancer in women who had used clomifene, this was just one of 20 separate comparisons in their subgroup analyses and was probably a chance association.

This study is important because it included 156 women with ovarian cancer, more than three times as many as any previous cohort study, and it compared infertile women who had used fertility drugs with infertile women who had not used fertility drugs. Although information on parity and use of oral contraceptives was unavailable for many women, analyses in the subgroup of women with this information suggested that adjusting for these variables would have had little effect on the results. However, although the study was much larger than previous investigations, it still could not exclude the possibility of a small increase in the risk of ovarian cancer in users of fertility drugs—the rate ratio for use of any fertility drug was 1.03, but the upper bound of the 95% confidence interval was 1.47.[3] Larger numbers of women will need to be studied to answer this question, and these will come with further follow-up of the cohort as they enter the age range where ovarian cancer is most common.

These data are reassuring and provide further evidence that fertility drugs do not increase a woman's risk of ovarian cancer to any great extent, although small increases in risk cannot be ruled out. Given the increasing numbers of women seeking fertility treatment,[11] this is important information for clinicians and their patients, and in a world where women increasingly turn to the internet for health information, clinicians should take time to discuss this matter so that women are properly informed. Some women who take fertility drugs will inevitably develop ovarian cancer by chance alone, but current evidence suggests that women who use these drugs do not have an increased risk of developing ovarian cancer.

1 Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet* 1971;2:163.
2 Cramer DW, Welch WR. Determinants of ovarian cancer risk II: inferences regarding pathogenesis. *J Natl Cancer Inst* 1983;71:717-21.
3 Jensen A, Sharif H, Frederiksen K, Kjaer SK. Use of fertility drugs and subsequent risk for ovarian cancer: Danish population based cohort study. *BMJ* 2009;338:b249.
4 Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:1184-203.

5 Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331:771-6.
6 Brinton LA, Moghissi KS, Scoccia B, Westhoff CL, Lamb EJ. Ovulation induction and cancer risk. *Fertil Steril* 2005;83:261-74.
7 Hughes E, Brown J, Collins J, Vanderkerckhove P. Clomiphene citrate for unexplained subfertility in women. *Cochrane Database Syst Rev* 2000;(1):CD000057.
8 Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, et al. Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 2004;103:1194-203.
9 Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Infertility, fertility drugs, and invasive ovarian cancer: a case-control study. *Fertil Steril* 1997;67:1005-12.
10 Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002;155:217-24.
11 Human Fertilisation and Embryology Authority. *Facts and figures 2006—fertility problems and treatment 2008.* www.hfea.gov.uk/docs/2008-10-08_Facts_and_Figures_2006_-_fertility_problems_and_treatment.pdf.

Preconception care

Public health campaigns are not reaching most women

FAYE NORMAN/SPL

RESEARCH, p 586

Camilla Bille visiting researcher, Epidemiology, Department of Public Health, University of Southern Denmark, 5000 Odense C, Denmark
Cbille@health.sdu.dk
Anne-Marie Nybo Andersen professor, Epidemiology, Department of Public Health, University of Southern Denmark, 5000 Odense C, Denmark

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:b22
doi: 10.1136/bmj.b22

Pregnancy has been called "a window of opportunity" for health promotion because it is thought to be the time when women are most willing to give up unhealthy habits. However, we should bear in mind that the focus for health promotion in pregnancy is the health of the developing child. In the linked study, Inskip and colleagues assess the degree to which 12 445 women aged 20-34 years recruited to the Southampton women's survey followed nutritional and lifestyle recommendations when planning a pregnancy.[1]

Sadly, the window often opens too late to provide sufficient care for pregnant women and offspring with special needs, or to start preconception supplementation to decrease the risks of adverse pregnancy outcomes that originate early in gestation. Daily folic acid supplements of 400 µg taken before conception and during organogenesis reduce the risk of a neural tube defect by 50-70%.[2] But the critical window begins before the woman knows she is pregnant, and the first antenatal visit usually occurs when organogenesis is complete. Thus, most women miss the opportunity to reduce the risk of congenital malformations.

Recommendations continuously change as new evidence emerges, so it is difficult for women to keep up with new information. Furthermore, some couples will have risk factors that are amenable to specific care around conception and pregnancy. For example, women with diabetes and poor glucose control during the first eight to 10 weeks of gestation have substantially poorer pregnancy outcome, including birth defects in the offspring, than those without diabetes.[3 4] These effects can be reduced with tight control of blood glucose, so women with diabetes or in high risk groups should have targeted care early on in pregnancy.

Over the past 20 years evidence has accumulated about the potential benefits of reaching women before conception. This has led to worldwide interest in including preconception care in prenatal prevention programmes.[5 6] In 2006, the Centers for Disease Control and Prevention published recommendations to improve preconception health care,[7] but little is known about how best to implement these recommendations.

Inskip and colleagues found that only 2.9% of women complied fully with prepregnancy recommendations about both alcohol and folic acid. Compliance, however, increased after pregnancy was recognised. At the prepregnancy interview, 44% of women who became pregnant reported taking any folic acid. When interviewed at 11 weeks' gestation 93% reported taking folic acid. At this time in pregnancy most organogenesis is complete. Most mothers to be want the best opportunities for their future child. If we assume that neglect is small, then Inskip and colleagues' results indicate that public health campaigns reach very few women in the target group. Most of the women reached by these campaigns are probably well educated, further contributing to the well documented social inequity in health in early life.[8-10]

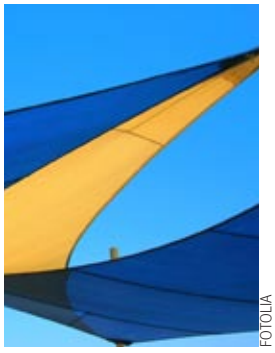
The timing and setting for public health campaigns aimed at improving conditions for the developing fetus need to be reconsidered. Men should also be targeted because their lifestyles affect semen quality and the health of their offspring.[11 12] In contrast to women, who over a decade of their life (preconceptionally, during pregnancy, and during breast feeding of two or three children) are supposed to follow the public health recommendations, recommendations for men are sparse. A healthier lifestyle among men around the time of reproduction and when raising their children might improve the paternal genome, provide a healthier upbringing for children, and improve women's compliance with recommendations.

Inskip and colleagues show that less than 77% of pregnancies in the areas studied (Southampton, United Kingdom) are planned. Efforts to prevent birth defects need to extend beyond traditional antenatal care. Preconceptional counselling would probably be beneficial as part of a scheduled preventive health programme, but couples would need to seek out and attend such programmes. Therefore, schoolchildren should be taught about reproduction, how to control and time pregnancy, and how to provide the best opportunities for the health of the next generation. We think that a school based public health strategy aimed at all young people would have the advantage of reaching everybody, regardless of their sex or whether they take part in preventive health visits.

1 Inskip HM, Crozier SR, Godfrey KM, Borland SE, Cooper C, Robinson SM; the Southampton Women's Survey Study Group. Women's compliance with nutrition and lifestyle recommendations before pregnancy: general population cohort study. *BMJ* 2009;338:b481.
2 Rush D. Periconceptional folate and neural tube defect. *Am J Clin Nutr* 1994;59(2 suppl):511S-5S.
3 Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care* 2005;28:323-8.
4 Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care* 2004;27:2819-23.
5 Atrash HK, Johnson K, Adams M, Cordero JF, Howse J. Preconception care for improving perinatal outcomes: the time to act. *Matern Child Health J* 2006;10(5 suppl):S3-11.
6 Boulet SL, Parker C, Atrash H. Preconception care in international settings. *Matern Child Health J* 2006;10(5 suppl):S29-35.
7 Johnson K, Posner SF, Biermann J, Cordero JF, Atrash HK, Parker CS, et al. Recommendations to improve preconception health and health care—United States. A report of the CDC/ATSDR Preconception Care Work Group and the select panel on preconception care. *MMWR Recomm Rep* 2006;55(RR-6):1-23.
8 Mortensen LH, Diderichsen F, Arntzen A, Gissler M, Cnattingius S, Schnor O, et al. Social inequality in fetal growth: a comparative study of Denmark, Finland, Norway and Sweden in the period 1981-2000. *J Epidemiol Community Health* 2008;62:325-31.
9 Villadsen SF, Mortensen LH, Nybo Andersen AM. Ethnic disparity in stillbirth and infant mortality in Denmark 1981-2003. *J Epidemiol Community Health* 2008 Oct 17 [Epub ahead of print].
10 Arntzen A, Mortensen L, Schnor O, Cnattingius S, Gissler M, Andersen AM. Neonatal and postneonatal mortality by maternal education a population-based study of trends in the Nordic countries, 1981-2000. *Eur J Public Health* 2008;18:245-51.
11 Brinkworth MH. Paternal transmission of genetic damage: findings in animals and humans. *Int J Androl* 2000;23:123-35.
12 Vine MF. Smoking and male reproduction: a review. *Int J Androl* 1996;19:323-37.

Sun protection in teenagers

Passive sun reduction strategies, such as shaded areas in schools, are valuable



FOTOLIA

RESEARCH, p 590

Elisabeth Thieden senior research scientist, Department of Dermatology, D92, Bispebjerg Hospital, University of Copenhagen, DK-2400 Copenhagen, Denmark
et01@bbh.regionh.dk

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:a2997
doi: 10.1136/bmj.a2997

In their cluster randomised controlled trial, Dobbinson and colleagues assess whether students in 51 secondary schools in Australia use or avoid newly shaded areas created by sun sails.[1] They found that a significantly higher number of students used the shaded areas during their lunch breaks in intervention schools. This shows that sun sails are a practical way of passively reducing sun exposure in teenagers. The results are encouraging, but it is hard to measure the benefit of the intervention because we do not know how many students used the shaded and unshaded outdoor areas or stayed indoors instead during the breaks.

The results are in line with a non-randomised controlled Swedish study in preschool children, in which situating the playground under a canopy of trees reduced ultraviolet radiation doses by up to 41%.[2] In Toowoomba, Australia, optimising the timing of morning and lunchtime breaks in schools has been estimated to reduce the dose of erythemal ultraviolet exposure by 45% (erythemal exposure is the ultraviolet exposure needed to produce a just perceptible redness of the skin in fair skinned people).[3] Another non-randomised comparison study found that postponing outdoor gardeners' 30 minute indoor lunch breaks, so that they started at noon rather than 11 30 am, reduced their daily dose of ultraviolet radiation by up to 10%.[4]

When devising sun protection strategies it is important to identify the situations in which different subgroups of the population can benefit most. For example, in Copenhagen, Denmark, adolescents receive most (68%) of their summer dose of ultraviolet radiation during the 16% of their days off during which they exhibit risk behaviour (defined as exposing the upper body or shoulders to the sun; table).[5] In addition, the adolescents did not apply sunscreen properly and were the age group with the largest number of sunburns.[6] The adolescents in this study received the lowest proportion of their ultraviolet radiation dose during school days, which was also true for British and Australian adolescents.[7 8]

Interventions to reduce sun exposure during weekends and holidays, especially in the middle of summer, are therefore more important than those focusing on exposure in schools. But because of the higher ambient ultraviolet radiation in Australia, interventions that passively reduce the radiation dose during weekdays are also valuable. In addition, teenagers all over the world who are exposed to high ultraviolet radiation doses on weekdays, such as those who do outdoor sport, should be identified and told how they can reduce their radiation dose.

In Denmark, traditional sun protection campaigns have not had the desired effect in teenagers. As with all other protective measures in this age group sun protection is most successful if a passive strategy is used.

When planning sun reduction strategies it is important to remember that the dose of ultraviolet radiation equals the intensity multiplied by the exposure time. An effective way to reduce the dose is therefore to reduce exposure time at times of the year and the day when ultraviolet radiation is highest.

Sunburn is most likely to occur in the beginning of summer because the skin loses its natural protection (pigmentation and stratum corneum thickness) during the winter.[9] The annual school curriculum should reflect this fact—outdoor sports, excursions, and field studies should take place mainly after the summer holidays.

Changes to daily time schedules that could passively reduce sun exposure include optimising break times, postponing morning songs or assembly until noon, and arranging outdoor sports classes to be early or late during the day. Attractive sitting and eating areas with water fountains or soda machines should be installed indoors; those installed outdoors should be under a canopy of trees, pergolas, or sun sails.

The detrimental effects of solar ultraviolet radiation are well known. The only established beneficial effect is the synthesis of vitamin D in the skin. The role of vitamin D on skeletal health is well established, but a

Distribution of the median percentages of total ultraviolet radiation* and exposure days received in a summer season of median 119 days[5]

Participants†	Work or school days				Days off work or school or holidays			
	Without risk behaviour‡		With risk behaviour‡		Without risk behaviour‡		With risk behaviour‡	
	Dose	Days	Dose	Days	Dose	Days	Dose	Days
Adolescents	11	36	2	2	19	42	68	16
Children	13	43	1	2	21	40	51	12
Indoor workers	17	55	1	1	33	35	36	8
Gardeners	51	54	4	2	41	25	9	4

*Standard erythema doses.
†346 Danish participants in a total of 39 068 days.
‡Defined as exposing the upper body or shoulders to the sun.

wide range of other major health benefits have been proposed, although they remain controversial. Virtually no data are available on the relation between personal exposure to ultraviolet radiation and vitamin D status. A recent meta-regression analysis showed no overall influence of latitude on vitamin D concentration but a widespread global insufficiency of vitamin D,[10] which is better counteracted by oral supplementation than by sunlight.[11 12]

New studies that document the effect of different interventions objectively—for example, by personal ultraviolet dosimetry or video recordings, as in Dobbinson and colleagues' trial—are needed as an evidence base for tailor made interventions to protect adolescents and other population subgroups from the sun.

1 Dobbinson SJ, White V, Wakefield MA, Jamsen KM, White V, Livingston PM, et al. Adolescents' use of purpose-built shade in secondary schools: cluster randomised controlled trial. *BMJ* 2009;338:b95.
2 Boldeman C, Dal H, Wester U. Swedish pre-school children's UVR exposure—a comparison between two outdoor environments. *Photodermatol Photoimmunol Photomed* 2004;20:2-8.
3 Parisi AV, Kimlin MG. Effect of meal break times on solar UV exposure of schoolchildren in a southeast Queensland summer month. *Environmetrics* 2000;11:563-70.
4 Thieden E, Collins SM, Philipsen PA, Murphy GM, Wulf HC. Ultraviolet exposure patterns of Irish and Danish gardeners during work and leisure. *Br J Dermatol* 2005;153:795-801.
5 Thieden E, Philipsen PA, Heydenreich J, Wulf HC. UV radiation exposure related to age, sex, occupation, and sun behavior based on time-stamped personal dosimeter readings. *Arch Dermatol* 2004;140:197-203.
6 Thieden E, Philipsen PA, Sandby-Møller J, Wulf HC. Sunburn related to UV radiation exposure, age, sex, occupation and sun bed use based on time-stamped personal dosimetry and sun behavior diaries. *Arch Dermatol* 2005;141:482-8.
7 Parisi AV, Meldrum LR, Kimlin MG, Wong JCF, Aitken J, Mainstone JS. Evaluation of differences in ultraviolet exposure during weekend and weekday activities. *Physics Med Biol* 2000;45:2253-62.
8 Diffey BL, Gibson CJ, Haylock R, McKinlay AF. Outdoor ultraviolet exposure of children and adolescents. *Br J Dermatol* 1996;134:1030-4.
9 Wulf HC, Sandby-Møller J, Kobayasi T, Gniadecki R. Skin aging and natural photoprotection. *Micron* 2004;35:185-91.
10 Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, et al. Global vitamin D level in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. *Osteoporos Int* 2009;20:133-40.
11 Young AR, Walker SL. UV radiation, vitamin D and human health: an unfolding controversy introduction. *Photochem Photobiol* 2005;81:1243-5.
12 Berwick M, Kesler D. Ultraviolet radiation exposure, vitamin D, and cancer. *Photochem Photobiol* 2005;81:1261-6.

Dopamine agonists and hyperprolactinaemia

Safety concerns must be supported by evidence before practice is changed

Niamh M Martin clinical senior lecturer and honorary consultant endocrinologist
n.martin@imperial.ac.uk
Tricia Tan consultant physician in metabolic medicine
Karim Meeran professor of endocrinology, Endocrine Unit, Department of Investigative Medicine, Imperial College Healthcare NHS Trust and Imperial College, London W12 0NN

Competing interests: None declared.
Provenance and peer review: Not commissioned; externally peer reviewed.

Cite this as: *BMJ* 2009;338:b381
doi: 10.1136/bmj.b381

Cabergoline and bromocriptine are both ergot based dopamine receptor agonists. Cabergoline has been used for the past 15 years to treat hyperprolactinaemia and is the first line treatment for prolactinomas. Despite its higher cost, cabergoline has largely superseded bromocriptine because of its greater efficacy in suppressing prolactin secretion, better tolerability, and more convenient dosing regimen. Recently, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning about the safety of these agents for treating hyperprolactinaemia amid concerns of an association with chronic pleuropulmonary, pericardial, and retroperitoneal fibrosis, and particularly fibrotic valvular heart disease.[1]

Cabergoline and bromocriptine—in common with other ergot based drugs such as ergotamine, methysergide, and the weight loss drugs fenfluramine and dexfenfluramine—bind to the serotonin receptor subtype 2B (5-HT_{2B}) located on heart valves. It has been proposed that activation of this receptor by these agents induces proliferation of valvular interstitial cells, leading to valvular heart disease. A large observational study and an echocardiographic prevalence study have recently confirmed that cabergoline is valvulopathic in doses given for Parkinson's disease.[2 3] Importantly, these studies show a significant association between higher cumulative doses of cabergoline and the severity of cardiac valvular regurgitation. Although bromocriptine is only a partial agonist at the 5-HT_{2B} receptor, it too has been associated with valvular heart disease.[4]

Naturally, the effect of cabergoline on heart valves reported in patients with Parkinson's disease has raised concerns about the safety of its use in the treatment of hyperprolactinaemia. However, it is difficult to extrapolate these results to patients receiving cabergoline for hyperprolactinaemia because they are typically younger, female, and taking much lower doses—typically 0.5-1 mg twice weekly, compared with 2-6 mg daily in Parkinson's disease. Although patients

with hyperprolactinaemia may take cabergoline for long periods, they usually stop taking it after the menopause. Also, periodic withdrawal of cabergoline in the treatment of prolactinomas after suppression of prolactin and shrinkage of the tumour may be a successful way to limit duration of exposure to these agents.[5] These strategies may limit the cumulative dose exposure.

Several recent cross sectional studies have investigated valvular heart disease in patients taking cabergoline for hyperprolactinaemia.[6-11] These studies do not support an association between treatment of prolactinomas with cabergoline and clinically significant valvular heart disease. However, mild[6 9] and moderate[7] tricuspid regurgitation, aortic valve calcification,[9] and mitral valve tenting[10] have been described. These studies are limited by their cross sectional design and relatively small number of patients. Longer term longitudinal studies in larger numbers of patients are currently lacking.

The recent MHRA guidance advises that cabergoline should not be used in pregnancy and must be stopped in women one month before trying to conceive. However, stopping treatment before planning a pregnancy may cause recurrence of hyperprolactinaemia and prevent ovulation. Pregnant women with larger prolactinomas should continue taking cabergoline because lactotrophs may enlarge during pregnancy and push the tumour towards the optic chiasm. Taking cabergoline during pregnancy has not been associated with miscarriage or fetal malformation.[12]

In light of current evidence and the recent MHRA guidance regarding the use of cabergoline in chronic endocrine conditions, what are the implications for patient care? Dopamine agonists such as quinagolide, terguride, and lisuride do not have 5-HT_{2B} receptor agonist activity and, therefore, may not induce fibrotic valvulopathy. However, before advocating these agents instead of cabergoline for the treatment of hyperprolactinaemia, we need evidence about the risk of fibrosis and their safety in pregnancy.

We support performing echocardiography before starting dopamine agonists for hyperprolactinaemia and during treatment. The frequency of this surveillance should be dictated by the dose of dopamine agonist used. Similarly, monitoring for pulmonary fibrosis with lung function testing and for retroperitoneal fibrosis as advised seems prudent. Collecting longitudinal data during this surveillance could help to ascertain the safety of bromocriptine and cabergoline. However, we are concerned that the current recommendation to avoid cabergoline before conception and during pregnancy lacks supporting evidence, and that adherence may have a negative effect on fertility in patients with hyperprolactinaemia.

1 Medicines and Healthcare Products Regulatory Agency. *Drug safety update*. Vol. 2, Issue 3, Oct 2008.
2 Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007;356:29-38.
3 Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007;356:39-46.
4 Serratrice J, Disdier P, Habib G, Viallet F, Weiller PJ. Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev* 2002;10:334-6.
5 Colao A, Di SA, Cappabianca P, Di SC, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 2003;349:2023-33.
6 Wakil A, Rigby AS, Clark AL, Kallvikbacka-Bennett A, Atkin SL. Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvular heart disease. *Eur J Endocrinol* 2008;159:R11-4.
7 Colao A, Galderisi M, Di SA, Pardo M, Gaccione M, D'Andrea M, et al. Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. *J Clin Endocrinol Metab* 2008;93:3777-84.
8 Bogazzi F, Buralli S, Manetti L, Raffaelli V, Cigni T, Lombardi M, et al. Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia. *Int J Clin Pract* 2008;62:1864-9.
9 Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, et al. Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *J Clin Endocrinol Metab* 2008;93:3348-56.
10 Lancellotti P, Livadariu E, Markov M, Daly AF, Burlacu MC, Betea D, et al. Cabergoline and the risk of valvular lesions in endocrine disease. *Eur J Endocrinol* 2008;159:1-5.
11 Vallette S, Serri K, Rivera J, Santagata P, Delorme S, Garfield N, et al. Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. *Pituitary* 2008 Jul 2 [Epub ahead of print].
12 Colao A, Abs R, Barcena DG, Chanson P, Paulus W, Kleinberg DL. Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. *Clin Endocrinol (Oxf)* 2008;68:66-71.

Amendments to the Coroners and Justice Bill

Concerns about data sharing may undermine doctors' and patients' confidence

Vivienne Nathanson director of professional activities, BMA, London WC1H 9JP
vivn@bma.org.uk

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:b895
doi: 10.1136/bmj.b895

Committee stage discussions in parliament are currently under way on the Coroners and Justice Bill. Although most of the clauses relate to amendments to the coronial system, clause 152 is receiving substantial attention in the press.

Clause 152 would allow all government departments to use a fast track procedure to share data without parliamentary debate. It includes a provision that allows ministers to "remove or modify any legal barrier to data sharing." The explanatory notes say that, "This could be by repealing or amending other primary legislation, changing any other rule of law (for example, the application of the common law to confidentiality to defined circumstances), or creating a new power to share information where that power is currently absent."

What does this mean for health data? Simply, it means a complete change in the current presumption of confidentiality for all identifiable patient data. If a minister "deemed it necessary to secure a relevant policy objective" and if "the order strikes a fair balance between the public interest and the interests of

any person affected by it" laws that currently limit the sharing of health data, including the Data Protection Act, could be set aside. Although it is difficult to postulate a good reason for removing the protections of the Venereal Disease Regulations and the provisions of the Human Fertilisation and Embryology Act, even these regulations would not be immune to the potential for removal.

Ministers say there are no current plans for such data sharing within health. In the early days of the bill, around the time of the second reading debate, reference was made to the need to share data for the purposes of medical research or in the case of an epidemic. The BMA does not recognise such a need. The sharing of data for medical research is covered by established good practice, shortly to be restated in a paper that follows the conclusion of the Walport and Thomas report. This enables release for medical research purposes if appropriate consent is given. The sharing of data during epidemics is already covered by the Notification of Infectious Diseases Regulations.

Health data are not privileged in the manner of legal information. But for many years they have been recognised as both special and sensitive. Research shows that patients expect that the health professional with whom they share information will hold it in confidence, and share it sparingly and on a need to know basis. Patients usually define those who "need to know" as people who offer them care who need to know some or all of their health data to do so safely and effectively. The General Medical Council is explicit about this requirement. Anecdotally, most of the ethics enquiries received by the BMA ethics advice team are about confidentiality and about the levels of reassurance that doctors can offer to their patients.

Legislation such as the Police and Criminal Evidence Act specifically requires that requests for a breach of confidentiality should come from a high level officer and leaves the decision to the senior clinician involved. Such breaches are specific to one patient, and they are granted if the information might help in the prevention or investigation of a serious arrestable offence.

Should patients, doctors, and other health workers be comforted by the requirement to balance the actions with the interests of those affected by it? The presence of all categories of data in the current draft suggests blindness to the special sensitivity of health data. Previous reports that other government departments, such as the Department for Work and Pensions, would like access to health data further undermine any reassurance.

Trust is fragile. Public trust in data security has been affected by the loss of laptops and information discs in the commercial sector and from government departments. There have been few such problems with health, but we have evidence that patients often ask general practitioners for reassurance that their details are not subject to such fragile security. If doctors also fear that protective laws could be repealed with little notice they will feel obliged to warn their patients; indeed they may be ethically and legally obligated to do so.

If the current draft legislation goes through with minimal changes, it could so undermine the confidence of doctors and patients in the future control of data that neither is willing to record the most sensitive information. The consequences for patient care are difficult to calculate. The consequences for medical research would be staggering—no researcher could be confident that the information they accessed was complete, and the potential to link rich data in ways that make a dramatic difference to the speed of epidemiological studies in the United Kingdom would be irretrievably damaged.

Bigger issues are also at stake here. It is not only health data that could be subject to these changes. Commentators have indicated that this "big brother" legislation gives governments unprecedented power of surveillance on all that we, as citizens, do and say. As citizens, doctors will doubtless have views on these powers as well—and support for the powers will vary. But there seems to be little difference of opinion on health data. The current provisions for exceptional sharing without patients' consent when genuinely necessary for public safety work well, and the hard won agreements to allow sharing of non-identifiable data for research is an important development. Ministers do not need swingeing new powers.

This week many of the leading medical organisations have written a joint letter to the justice secretary seeking the complete removal of health data from the provisions of the bill. We are seeking a meeting to provide him with the reasons behind our concerns and to emphasise why we can see no problems in the health sector to which this legislation is an acceptable solution.

1 Thomas R, Walport M. Data sharing review report. Ministry of Justice, 2008. www.justice.gov.uk/publications/data-sharing-review-consultation.htm.
2 NHS Information Authority. Share with care! People's views on consent and confidentiality of patient information. Birmingham: NHSIA, 2002.
3 General Medical Council. Confidentiality: protecting and providing information. 2004. www.gmc-uk.org/guidance/current/library/confidentiality.asp.
4 Home Office. Police and Criminal Evidence Act 1984. http://police.homeoffice.gov.uk/operational-policing/powers-pace-codes/pace-code-intro/.