WOMEN'S health update

Concerns about patient safety in osteoporosis clinical trial

Gill Sanson, author of The Myth of Osteoporosis reports on an osteoporosis clinical trial taking place in Aotearoa New Zealand. Her research shows the trial document overstates the risk of osteoporosis and the benefits of the trial drug zoledronate, and understates the potential harms of participating in the clinical trial.

Osteoporosis is controversial

Once a relatively rare condition of fragile bones that afflicted mostly the very elderly, osteoporosis became commonplace when it was re-defined as a measure of low bone density in 1993. Since then sustained persuasive marketing campaigns portraying osteoporosis as a silent and deadly epidemic, have ensured that most women over 50 have a fear of developing fragile bones later in life. Prevention of osteoporosis was one of the primary reasons millions of women took long-term hormone replacement therapy until evidence of serious adverse events reversed this application in 2002.

These days millions of women worldwide take osteoporosis bisphosphonate drugs like zoledronate, and there is a trend towards treating younger women with mildly reduced bone density or pre-osteoporosis (osteopenia) - potentially half the world's post-menopausal women. Medicating vast numbers of healthy women in the hope of preventing fractures in 20 or 30 years time is, in the words of U.S. osteoporosis authority Susan Ott "based on hope rather than evidence, and several editorial reviews have concluded that these women do not need drug therapy."[1]

Osteoporosis Clinical Trial

Selected from the electoral roll, New Zealand women aged 50 to 60 are being mailed an invitation to participate in the University of Auckland Faculty of Medical and Health Science's ten-year 'Zoledronate and fracture prevention in early postmenopausal women' clinical trial. Funded by the Health Research Council and approved by the Health and Disability Ethics Committee (HDEC) in 2011, the trial will measure the occurrence of morphometric spinal fractures – typically fractures with no symptoms identified by x-ray and determined by a loss in vertebral body height. The 1050 women participants with normal or mildly low bone mineral density will be assigned either a 5mg intravenous infusion of zoledronate or placebo at the start of the trial and again after 5 years. They will also have repeated bone density scans and x-rays of the spine.

While acknowledging that osteoporosis is a serious concern in the frail elderly and those with underlying medical conditions, it is difficult to understand why a trial of younger well postmenopausal women is considered advisable when repeated studies of osteoporosis treatments in this age group have shown little or no benefit. The incidence of fractures in this population is so low (around 1% a year), that it is estimated up to 270 women might need to be treated for 3 years so that one of them could avoid a single vertebral fracture.[2,3] A low baseline risk automatically means much smaller absolute benefits from long-term drug treatment and a much higher risk-to-benefit ratio.

The Participant Information Sheet received by the targeted women offers justification for the trial and reassurances regarding the safety and effectiveness of zoledronate. But we are concerned that the facts supplied are incomplete and confusing, and that healthy women are committing to a long-term trial without understanding the complexity of the issues or being fully informed of potentially very serious risks.

Statements in the Participant Information Sheet (in bold below) could be exaggerating the risk of osteoporosis, overstating the benefits of zoledronate, and downplaying its harms:

1. About 50% of women will sustain a fracture due to osteoporosis after the age of 50.

Fracture statistics in Western countries are widely divergent. When characterised as bones that fracture easily (typically the hip, wrist and vertebrae), osteoporosis is uncommon in women under the age of 80. Hip fractures, by far the most serious fractures, occur mostly in the very elderly. A large US study found that over 15 years, 18% of women aged 68 to 84 had a spinal fracture.[4] The majority of these fractures are not painful clinical fractures – some two thirds of women who have spinal fractures are unaware of the fact and have no symptoms.[5]

2. Low bone density is a strong predictor of fracture risk.

Several large studies have now established

Continued on page 2

VOL 17 NO 2 JUNE 2013

INSIDE:

Women's Health Update features women's health news, policy and scientific findings, to enable health care professionals and community-based workers to be at the forefront in women's health.

Women's Health Update is published by the Women's Health Action Trust.

Continued from page 1

that low bone density is not a good predictor of fracture. A U.S. study of almost 150,000 postmenopausal Caucasian women aged 50 to 104 years found that 82 percent of the (2,259) women who fractured over one year did not have a bone density diagnosis of osteoporosis.[6]

3. Zoledronate... effectively prevents fractures - in a recent study of 8000 women with osteoporosis zoledronate decreased the risk of spine fractures by 70% and hip fractures by 40%.

Using percentages that give relative rather than absolute risk reduction can make treatments look more effective than they are. In the zoledronate study of higher-risk older women the absolute risk reduction of spinal fractures was 7%, and hip fractures, 1%.[7] In other words, 13 at risk women would need to take the drug for 3 years to prevent one spinal vertebral fracture; and 91 women would need to take zoledronate for 3 years for one of them to avoid a hip fracture.[8] An extension of the study found that zoledronate reduced morphometric spinal fractures but not more serious clinical spinal fractures after 6 years.[9]

4. It is likely that treatment with... zoledronate will safely prevent bone loss. ...zoledronate may also prevent fractures with the benefits persisting well beyond the treatment course.

Bisphosphonate drugs suppress the normal bone remodeling process and have been shown to increase bone density in the short term. The pharmacology of bisphosphonates is not fully understood, and the long-term effects are unknown. Almost all the available data comes from patients who have taken them for less than 5 years.

Zoledronate, approved by the U.S. Food and Drug Administration (FDA) in 2006 and administered as an infusion, is the newest and most potent member of the bisphosphonate family. It is possible to achieve profound and sustained suppression of bone turnover with a single low dose of zoledronate, which explains its five-yearly administration in the trial.[10] The drug stays in the body and is permanently incorporated into bone, exposing patients to an accumulative effect for at least 10 years after treatment ceases. There is no way of removing it should adverse events occur.

Evidence is growing that the bisphosphonate's action of suppressing bone turnover may cause bone to deteriorate in strength and become more brittle and prone to fracture. Although causality has not been established, the incidence of serious atypical fractures of the femur (thigh bone) has been found to increase progressively with the duration of bisphosphonate use, and is significantly higher after 5 years compared with less than 3 years.[11] These fractures occur with no impact or warning, and healing can be impaired because bone remodeling has been suppressed.[12]

The trial Participant Information Sheet acknowledges this risk but maintains *'there is not convincing evidence that this is a problem with zoledronate.'* The document fails to mention that in 2010 the FDA added a warning to zoledronate's labeling and informed the manufacturer Novartis "your medication guide must include information about the serious risk of atypical subtrochanteric and diaphyseal femoral fractures."[13,14]

Neither does the trial document mention the FDA's 2009 and 2011 label warnings of the risk for severe musculoskeletal pain (which can persist for years); and for kidney failure, following 16 deaths from acute renal failure following zoledronate infusion.[15,16] The trial document does inform participants they will be screened for kidney disease, and does mention zoledronate's risk for inflammatory eye disease and, in higher doses, rare (but catastrophic) osteonecrosis (bone death) of the jaw.

New Zealand women participating in the Auckland University trial may be doing so pointlessly. And given the limited information offered they are unlikely to be fully aware of the risks or realise that in 10 or more years time the zoledronate infusions may cause the very condition they are supposed to prevent. The FDA label warnings raise questions as to how the zoledronate trial gained unqualified ethics approval. The HDEC Northern X Committee advised the Principal Investigator on November 15th 2011 that there were "no significant ethical issues", and recommended: "In the benefits section [of the Participant Information Sheet], it will help to say it is safe...".[17]

1. Ott, S.M. What is the optimal duration of bisphosphonate therapy? *Cleveland Clinic Journal of Medicine* 2011 vol. 78 9 619-630

2. Miller PD., et al. An approach to identifying osteopenic women at increased short-term risk of fracture. *Archives of Internal Medicine* 2004;164:1113-20.

3. Alonso-Coello, P. et al Drugs for pre-osteoporosis: prevention or disease mongering? *BMJ 2008*;336:126

4. Cauley, J. A., et al.. Long-term risk of incident vertebral fractures. *JAMA* 2007 298(23): 2761-2767.

5. Ibid

6. Siris, ES et al. "Bone mineral density thresholds for pharmacological intervention to prevent fractures." *Archives of Internal Medicine*. 2004;164:1108-1112.

7. Black DM, et al Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007 May 3;356(18):1809-22.

8. B. Cortet. Absolute risk reduction to compare efficacy of antiosteoporotic treatments in the absence of head-to-head trials. *Medicographia*, 2010; 32,1

9. Whitaker, M. et al Bisphosphonates for Osteoporosis — Where Do We Go from Here? *N Engl J Med* 2012; 366: 2048-205

10. Bock, O,. Felsenberg, D. Bisphosphonates in the management of postmenopausal osteoporosis – optimizing efficacy in clinical practice. *Clinical Interventions in Aging*. 2008; 3(2): 279–297

11. Ott, S.M.

12. Kennel, K.A., Drake, M.T. Adverse Effects of Bisphosphonates: Implications for Osteoporosis Management. *Mayo Clinic Proceedings*. 2009; 84(7): 632–638.

13. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm229244.htm

14. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM229242.pdf

15. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm229244.htm

16. http://www.fda.gov/Drugs/DrugSafety/ucm270199.htm

17. http://ethics.health.govt.nz/about-committees/archived-minutes-and-reports-pre-2012/northern-x-committee

Surgical Mesh: More questions than answers

Following recent media attention and a number of enquiries to Women's Health Action, Policy Analyst, Sandy Hall, researched the latest information about surgical mesh. Her findings raise a number of questions and concerns about the use of mesh in uro-gynaecological surgery.[1]

It is now clear that both in Aotearoa New Zealand and internationally significant numbers of women have experienced complications ranging from moderate discomfort to disabling pain and severe tissue damage as a result of surgical mesh implants. So what is surgical mesh and should we be using it in Aotearoa New Zealand?

Surgical mesh is a medical device that is used to provide additional support when repairing weakened or damaged tissue. Manufactured from permanent (non-dissolving) materials usually either polypropylene (synthetic) or pig collagen (biological) or a composite of both, mesh is used in place of, or in addition to sutures for surgical repair. The benefits are described as including shorter surgery times and more durability.

First used in the 1950s for hernia repair, meshes have been used for the repair of uterine and vaginal wall prolapse (pelvic organ prolapse or POP) and urinary incontinence for more than a decade. Backed by only limited research data, surgical mesh was aggressively promoted and rapidly adopted by many gynaecologists within Europe and later the USA.

As early as 2008, prompted by increasing numbers of reports of complications particularly after uro-gynaecological surgery, the US Food and Drug Administration (FDA) began issuing safety warnings regarding the use of the mesh. By 2011 the FDA stated it had serious concerns over the use of vaginal mesh for the treatment of vaginal prolapse and incontinence.[2] Among its concerns were that existing studies were poorly designed and documented, and research timeframes too short to establish clear proof of its

effectiveness. It notes that the use of mesh has not been *"proven to provide better outcomes and that serious complications including infection, pain, incontinence, perforation of bowel or bladder, are not rare"*.[3]

In their October 2011 newsletter, the Auckland Women's Health Council (AWHC) highlighted a number of concerns about the use of gynaecological mesh in New Zealand. In particular they noted work by Professor Julie Quinlivan who has described the horrendous and permanent disfigurement involved after attempts to remove the gynaecological mesh and who has also described how some medical devices are able to avoid having to undergo clinical trials before they are cleared by the FDA and marketed – including surgical mesh.[4] Indeed the FDA itself notes *"Clinical performance data typically has not been used to support clearance for POP or SUI uro-gynaecologic mesh products."* [5] Furthermore, Professor Quinlivan noted that there is no requirement for medical devices to be approved by any overseas medical device regulator before they can be supplied in New Zealand.[6] A further AWHC article in 2012 notes that Medsafe senior advisor Robert Jelas has stated *"New Zealand relies on medical device regulators in countries with 'robust pre-market approval schemes' such as Canada, Australia and the European Union"*.

Over the past months a number of stories have also appeared in The New Zealand Herald with further examples of the problems caused by mesh implants in both men and women.[7] According to The Herald there have been 600 claims to the Accident Compensation Corporation (ACC) involving meshes between 2008 and 2012. The post surgical complications included erosion through the vaginal epithelium, infections, severe pain, urinary problems, recurrence and/or incontinence, bowel, bladder and blood vessel perforation during insertion, and the requirement for additional surgical procedures. Just fewer than 400 claims have been accepted.[8]

Like AWHC, The Herald also found that health authorities were standing by the use of surgical mesh[9] despite evidence of complications. Recent information on Medsafe's website states *"Medsafe has concluded that surgical mesh is safe when used in accordance with the manufacturers' instructions by an appropriately trained surgeon. This conclusion is in line with that of other device regulators and professional bodies. Medsafe notes that surgical mesh remains approved for use by medical device regulators globally"*.[10] Similarly, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, acknowledges FDA warnings but supports its use, suggesting post-operative care, rather than the mesh itself, may be the cause of complications.[11]

The Herald quoted a local surgeon who argues that the use of mesh to repair hernias of the abdominal wall is usually a "good procedure" with a low complication rate. However, he also questions the approval process and suggests because of success in abdominal wall repairs, manufacturers and the FDA wrongly assumed mesh could also be used for genital prolapse in women *"Mesh in the abdomen behaves very differently to the mesh in the vagina, which is never sterile... They* [the FDA] *assumed it would work the same so they approved it without proper research and clinical trials"*.[12]

This position is taken up in several recent journal articles which suggest that both where mesh is used and who uses it, is of concern.[13] Information published by the Australian and New Zealand College of Gynaecologists emphasises the importance of specialist training for operating surgeons, informed consent including discussion of alternatives, and for surgeons to be up-to-date on the latest practice literature and potential complications. The College suggests that when mesh is used in newer procedures it should only be in the context of a conducted clinical trial with proper ethics and consent procedures. Sadly, journal articles, media reports and our contact with women who have experienced complications suggest that this advice is not always followed.

In the US and Australia there are now thousands of lawsuits underway. The FDA received reports of neuromuscular problems, vaginal scarring or shrinking, and three deaths directly related to mesh replacement and now encourages health care providers to recognise *"that in most cases, POP can be treated successfully without mesh, thus avoiding the risk of mesh-related complications."* It also noted that mesh placed abdominally for POP repair *"may result in lower rates of mesh complications compared to transvaginal POP surgery with mesh."* [14] In July 2011 the FDA issued a warning that vaginal mesh products are associated with significant morbidity without conclusively improving outcomes compared with traditional native tissue repair. The FDA now *"encourages health care providers to recognize that in most cases, POP can be treated successfully without mesh, thus avoiding the risk of mesh-related complications."* Specialists in the USA have decreased their use of mesh for pelvic organ prolapse repair, according to a recent survey.

Despite the overseas reports of significant complications, increasing concern expressed by the FDA, questioning by increasing numbers of consumers, women's organisations, and many medical professionals, and growing complaints, mesh is still being implanted in hundreds of New Zealand women. Women we spoke with report not being warned about possible complications and risks by their surgeons and finding insufficient up to date information on the Medsafe website about mesh or the risks.

We believe the use of surgical mesh raises the following questions and concerns:

- In light of the FDA warnings should the use of mesh in uro-gynaecological surgery been discontinued until clear evidence of its effectiveness and safety is produced?
- The lack of support reported by women who have suffered complications after the use of surgical mesh highlights systemic gaps in both follow-up and compensation that warrant further investigation.
- Why are the qualifications and experience required of surgeons using mesh not made clear to the public via a specialist registry for example?
- Why hasn't a robust informed consent process been developed to ensure more information is provided to all prospective patients about the risks involved and the alternatives available?
- Why are there no specific Aotearoa New Zealand based systems in place to monitor its use?
- If information about the effectiveness of medical devices is not necessarily based on robust clinical trials or approval processes, how can health care consumers tell which products have been properly tested and approved and which have not? The role Medsafe should play in approving medical devices and providing up to date information also requires further examination. In particular, whether Medsafe's approval procedures for medical devices in Aotearoa New Zealand should ever rely solely on overseas evidence.

Continued on page 4

SAVE THE DATE

This year marks 120 years of women's suffrage. In 1893, Aotearoa New Zealand became the first nation in the world to grant women the right to vote. Women's Health Action celebrates and reflects on the past 120 years at our annual Suffrage Breakfast, 19th September at Alexandra Park, Greenlane, Auckland. Tickets on sale soon.

Continued from page 3

While many patients will experience no side effects the women we talked to told us the effects of complication from the use of surgical mesh can be long term and life changing. There are also clear and specific concerns documented in the conventional medical literature. We suggest it is time for health authorities to put the consumer first and intervene in the use of surgical mesh in Aotearoa New Zealand. As there are existing treatment alternatives the evidence suggests that suspending the use of surgical mesh in uro-gynaecological procedures pending further investigation is warranted.

If you have experienced problems as a result of treatment using surgical mesh you can contact WHA at info@womens-health.org.nz or call 09 520-5295.

1. This article focuses on the use of mesh for gynaecological surgeries only. We are however aware of reports that problems have also occurred for both men and women after mesh use in hernia repair.

2. FDA 2011 *Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse.*

3. Royal College of Obstetricians and Gynaecologists. *"The Use of Mesh in Gynaecological Surgery."* Scientific Advisory Committee Opinion Paper 19. April 2010.

4. http://www.womenshealthcouncil.org.nz/site/aklwhc/files//OCTOBER%202011.pdf

5. *FDA 2011 Urogynecologic Surgical Mesh*

6. Medicines Act 1981

7. http://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=10837440

8. Ibid

9. http://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=10838873

10. http://www.medsafe.govt.nz/Consumers/devices/UrogynaecologicalSurgicalMeshImplants.asp

11. http://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=10838873

12. Ibid

13. RANZCOG College Statement: C-Gyn 20

14. Royal College of Obstetricians and Gynaecologists Scientific Impact Paper No. 19 4 of 5

Women's Health Action Presents the Big Latch On 2013

By Maggie Behrend

VENUE REGISTRATIONS ARE NOW OPEN FOR THE BIG LATCH ON – FRIDAY AUGUST 2ND, 2013!

Each year, Women's Health Action proudly coordinates the Big Latch On. Initiated in 2005 by Women's Health Action to celebrate World Breastfeeding Week in Aotearoa New Zealand, the event involves women coming together at registered venues across the country to latch on (breastfeed) their children at the same time. The purpose of the event is to normalise breastfeeding, raise awareness about the benefits of breastfeeding, and encourage women to form support networks.

In line with World Breastfeeding Week 2013, the theme for this year's Big Latch On is 'Breastfeeding Support: Close to Mothers', which highlights the importance of support in the home and in the community for breastfeeding women.

The Big Latch On 2013 will take place at 10:30am on Friday, August 2nd. If you would like to coordinate an event in your area, registrations are now open online at: www.womens-health.org.nz. Events can be as small as two people, or as large as a whole community! If event coordination isn't your thing, you can still attend – look for registered venues in your area through the link above.

For more information, email Lee at breastfeeding@womens-health.org.nz

NOTICEBOARD

WOMEN'S HEALTH ACTION'S ANNUAL SUFFRAGE BREAKFAST
19 SEPTEMBER, 7–9AM - AUCKLAND
Registrations open soon. Contact info@womens-health.org.nz or phone 09 570 5795 for more information.

BIG LATCH ON
2 AUGUST - ACROSS AOTEAROA NEW ZEALAND

CHILDREN, CHILD MALTREATMENT AND INTIMATE PARTNER VIOLENCE: RESEARCH, POLICY AND PRACTICE - CONFERENCE
5 JUNE - WELLINGTON
Co-hosted by Families Commission and New Zealand Family Violence Clearinghouse the conference will feature international keynote speakers Professor Jeffrey Edleson and Sudha Shetty and Aoteara New Zealand keynote speaker Di Grenell.
www.nzfvc.org.nz/?q=node/885

AUCKLAND PHA BREAKFAST WITH DEPUTY MAYOR PENNY HULSE
5 JUNE 7:30–9AM - AUCKLAND
Penny Hulse will discuss Auckland Council's vision for a healthy city and respond to questions. Contact Maggie@womens-health.org.nz or phone 09 520 5295 to register.

WHAKAWHETU AND TAHA CONFERENCES
20-21 JUNE - AUCKLAND
Whakawhetu and TAHA have partnered to provide back to back conferences that aim to inspire further development and on-going action to improve health outcomes for Māori and Pacific pregnancies and babies.
www.whakawhetu.co.nz/

HE MANAWA WHENUA - INDIGENOUS RESEARCH CONFERENCE 2013
30 JUNE–3 JULY - HAMILTON
Organised by Te Kotahi Research Institute in conjunction with The University of Waikato
www.nzfvc.org.nz/?q=node/860

HEALTH PROMOTION FORUM SYMPOSIUM
4-5 JULY - WELLINGTON
The symposium will provide an opportunity to draw on our experience, explore ideas and work together to envisage a new future for health promotion here in Aotearoa New Zealand.
www.hpforum.org.nz/a-generation-from-now-2013.html

FAMILY PLANNING CONFERENCE 2013: POSITIVE SEXUAL HEALTH
31 OCTOBER–2 NOVEMBER - WELLINGTON
The conference has four streams: Clinical and personal health, health promotion and sexuality education, advocacy, international. There are five themes: Positive sexuality, young people, contraception, sexually transmissible infections, abortion.
www.familyplanning.org.nz/conference

Women's Health Update is produced by Women's Health Action Trust.
To receive copies of *Women's Health Update,* make suggestions about future contents or send items for publication please contact: Women's Health Action Trust, PO Box 9947, Newmarket, Auckland 1149, NZ. Ph (09) 520 5295, Fax (09) 520 5731, email: info@womens-health.org.nz
Women's health information - www.womens-health.org.nz
Breastfeeding Friendly Workplaces - www.bfw.org.nz

MINISTRY OF HEALTH

ISSN 1174-7692 (Print)
ISSN 2324-1845 (Online)