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Review

Contraception for teenagers and young adults with cancer

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Abstract

Adolescence can be an extremely stressful time for all concerned. When this period is then compounded by the development of cancer, formidable and seemingly insurmountable problems may be perceived. Cancer in adolescence is relatively uncommon, with an annual incidence rate in western populations of approximately 150–200 per million. Five-year survival of patients diagnosed around 1990 exceeded 70% in the United Kingdom (UK) and United States of America (USA), and adolescents with cancer are likely to remain fertile. Further advances in therapeutic modalities are creating a generation of adolescents and young adults with cancer who can now aspire to the same sexual and reproductive activities as their healthy peers. This then raises the issue of avoidance of undesired pregnancy during and after treatment. This article aims to address the contraceptive needs of adolescents and young adults undergoing treatment for cancer.

Keywords: Adolescence; Cancer; Contraception; Teenager; Pregnancy

1. Introduction

Adolescent sexuality is often a topic of difficulty for health professionals and parents alike. Yet, the median age for first sexual intercourse is 16 years in most of the industrialised countries (e.g., United States of America (USA), Canada, United Kingdom (UK), France, The Netherlands, and Sweden) [1]. Ten percent of French 15 year-old teenagers have had sexual intercourse [2]. In Britain, 30% of boys and 26% of girls aged 16–19 years report their first heterosexual intercourse younger than 16 years [3].

Cancer in adolescence is relatively uncommon. However, after a decreasing incidence from the peak in early childhood until 9 years of age, it steadily increases through adolescence, with an incidence of 206.8 per 1 million for the 15–19 year-old group in the United States between 1990 and 1997. Adolescent cancer accounts for 5% of deaths in the United States between 15 and 19 years of age [4]. The most frequent cancers in adolescents and young adults are Hodgkin's disease, germ-cell-tumours, leukaemia, cancers of the central nervous system, non-Hodgkin's lymphoma, non-rhabdomyosarcoma soft-tissue sarcomas, Ewing's tumours, osteosarcoma, thyroid cancers and melanomas [4,5]. Survival rates have improved over the past decades, with the use of combined surgery, radiation and dose-intensive combination chemotherapy. It has been estimated that by the year 2010, 1 in 250 young adults (20–29 years) will be long-term survivors of childhood cancer [6].

A range of factors influence the degree and nature of fertility defects in children and adolescents with cancer, including age, tumour site, treatment modality and gender. The most important study which investigated 2283 adult survivors of childhood and adolescent cancer in five centres, showed a relative risk of fertility of 0.93 for females and 0.76 for males. Alkylating agents and

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sub-diaphragmatic radiation were deemed most likely to impair fertility [7]. Cancer therapy may induce amenorrhoea, the onset and duration of which depends on the age of the patient, type, intensity and duration of treatments. Nevertheless, many adolescents undergoing treatment for cancer remain fertile [7].

Except for the extremely ill, adolescents with chronic conditions have the same sexual and marital aspirations as healthy adolescents, and it can be assumed that those in whom pubertal development and peer relationships are relatively unencumbered will have sexual behaviours similar to their peers [8–10]. Furthermore, adolescents with cancer and who have had cancer face developmental issues in terms of independence and separation from their parents, health concerns and questions about their fertility potential. These complex issues may encumber their sexual education and their perception of information on sexual health and contraception.

Given that young people with cancer and teenagers who survived childhood cancer are likely to remain fertile, and have the same sexual behaviour as healthy teenagers, they share with their peers the same need for effective contraception and information about sex to avoid unwanted pregnancies and prevent sexually transmitted infections (STIs). Many cytotoxic drugs, as well as radiotherapy, are teratogenic and mutagenic and conception during chemotherapy may result in abortion of the embryo, or in gross congenital abnormalities of the foetus, thus emphasising the need for effective contraception in sexually active young people undergoing treatment for cancer [11].

Advances in therapeutic modalities for adolescents with cancer (including solid tumours as well as haematological malignancies) means that they can aspire to the same sexual and reproductive health activities as other healthy adolescents and young adults. However, this aspiration can and does raise several medical and educational issues. We are not aware of any publications on this subject, and this article reflects on these issues and suggests possible solutions.

2. Contraceptive methods and their use in young people with cancer

Several contraceptive methods are available and summarised in Table 1, although the effectiveness of the different methods in teenagers is unknown.

Table 1
Contraceptive methods

Abstinence
Natural methods
No methods
Withdrawal
Periodic abstinence
Oral contraception
Oral combined pill (OCP)
Progestin-only pill
Emergency contraception (morning-after pill)
Injectable contraceptives (Depo-Provera®)
Implant contraceptives (Norplant®, Jadelle®, Implanon®)
Intra-uterine device (IUD)
Barriers methods
Female barrier methods (diaphragm, cervical cap, vaginal sponge, female condom, vaginal spermicides)
Male condoms

2.1. Abstinence

Abstinence or postponement of sexual activity is the most effective method of preventing pregnancy and sexually transmitted infections (STIs) [12,13]. For some teenagers and young adults with cancer, abstinence is common, normal and acceptable. However, it needs to be recognised that they may have a sense of not having time enough to postpone a sexual relationship with their partner. It is difficult to add the loss of a potential sexual life to the many other restrictions these patients face, and it may be important for a teenager facing death to have experienced a sexually fulfilling relationship before dying [14].

It is therefore difficult to recommend abstinence as a contraceptive method for these very special patients, unless they are strongly motivated and willing to use it.

2.2. No method/withdrawal/periodic abstinence

2.2.1. No method

It has been reported that as many as 25–50% of sexually active adolescents in the United States do not use contraception at first intercourse. As far as teenagers are concerned, it is far more convenient not to use any method of contraception. However, such an approach to sexual activity leads to a very high risk of acquiring STIs, HIV transmission, and getting pregnant (85% in the first year) [15].

Young people with cancer should be strongly advised to use an effective method of contraception at all times.

2.2.2. Withdrawal

Remains a common method used by teenagers, especially within the first year of becoming sexually active. Effectiveness of withdrawal (or *coitus interruptus*) depends on the man's ability to withdraw the penis before ejaculation. First-year failure rates approach 24%, and there is a risk of STIs and HIV transmission [15].

Although it is a free and convenient method, it should not be recommended as a method for teenagers, in particular for those with cancer.

2.2.3. Periodic abstinence

Relies on abstaining from sexual intercourse during the fertile window during which sexual intercourse can result in pregnancy. This "fertile window" consists of the five days before ovulation and the day of ovulation itself and can be identified by observing changes in cervical secretions, monitoring increases in basal body temperature or using calendar calculations [16–18]. However, even normal healthy women with usually regular menstrual cycles have been shown to have highly unpredictable fertile windows based on clinical guidelines, resulting in a typical failure rate as high as 25% [19]. The method does not prevent STIs and HIV transmission [15].

Not only is this an unreliable method for many female adolescents who have irregular cycles, but it is a much more inadvisable contraceptive method for those with cancer, whose cycles may be more irregular with chemotherapy, and who may suffer from febrile infections, thus making basal temperature monitoring impossible.

2.3. Non-barrier methods

2.3.1. Oral contraception

2.3.1.1. The oral combined pill (OCP). The combined oral contraceptive pill (OCP) contains both synthetic oestrogens and progestin, and prevents ovulation by inhibiting gonadotropin-releasing hormone. Additionally, progestin-induced changes such as increased cervical mucus viscosity, endometrial atrophy and changes in tubal transport mechanism provide secondary contraceptive mechanisms. There are many brands used throughout the world, containing 15, 20, 30, 35 or 50 μg of ethinyl oestradiol as the oestrogen. Mestranol is now rarely used. Several generations of progestins are used; first generation (ethynodiol diacetate, norethindrone acetate, norethindrone), second generation (norgestrel, levonorgestrel) or third generation (desogestrel, norgestimate, gestodene). OCPs are either monophasics, which contain a constant amount of hormones, or multiphasics (biphasic or triphasics), which vary the amount of progestin, and sometimes oestrogen, over the course of a 21 day-cycle [2,13,20]. OCPs containing third generation progestin are more expensive and may therefore be more difficult to obtain.

The OCP is the most widely-used contraceptive method for teenage girls, often used by as many as 35% of girls under 16 years, and by 50% of girls aged 16–19 years attending family planning clinic in England in 2001–2002 [21]. OCPs, especially those with low dose oestrogen, are only effective if used consistently and correctly. The typical failure rate of OCPs in adults is 3% [22], and in adolescents 5–15% [23]. While adolescents are less compliant than adults, with over half of them stopping the pill during the first year of use [24], OCPs carry no additional risks when started in young teenagers with established periods compared with women in their 20s [21].

Medical eligibility criteria have been published for the use of contraceptive methods by the World Health Organization (WHO) [25]. The conditions affecting eligibility for the use of each contraceptive method (including OCPs) were classified under one of the following four categories:

1. A condition for which there is no restriction for the use of the contraceptive method.
2. A condition where the advantages of using the method generally outweighs the theoretical or proven risks.
3. A condition where the theoretical or proven risks usually outweigh the advantages of using the method.
4. A condition which represents an unacceptable health risk if the contraceptive method is used.

The only malignancy in which the use of OCPs is absolutely contraindicated is breast cancer. The WHO medical eligibility criteria apply to adolescents as well. Nevertheless, OCP prescription for young people with cancer involves far more specific issues than the issues common to healthy teenagers. For young people receiving chemotherapy and/or radiotherapy, complicating factors include:

(a) Thrombocytopenia. Chemotherapy may induce thrombocytopenia, the nadir, duration and time of onset of which depends on the drug regimen and protocol, with the critical issue being the control of menstrual flow. Patients with a predictable short course of thrombocytopenia usually do well on cyclic monophasic OCPs. OCPs can be given throughout treatment and usually induce an atrophic endometrium with minimal bleeding. If breakthrough bleeding occurs during the platelet nadir, OCPs can be increased to up to four pills a day to prevent excessive bleeding, and, when bleeding is controlled, the pills may be decreased by a single-pill at a 3-day interval. For the OCPs provided in 28-days packs, omission of placebo pills will avoid bleeding, and patients may take continuous monophasic pills without bleeding [26].

For patients in whom severe and/or prolonged thrombocytopenia can be expected, cyclic OCP use should not be recommended. Continuous monophasic OCPs could be suitable, given good compliance and the absence of gastrointestinal side-effects (cf below).

(b) Gastrointestinal tract side-effects Chemotherapy-induced vomiting and mucositis may significantly reduce the absorption of OCPs. Changes in gastrointestinal (GI) bacterial flora may occur following chemotherapy-induced diarrhoea. Infection or repeated courses of antibiotics in febrile neutropenic patients may result in

changes in gastro-hepatic circulation with decreased effectiveness of OCPs [26].

For teenagers and young adults undergoing highly emetogenic and aggressive chemotherapy with anticipated severe gastrointestinal side-effects, use of OCPs cannot be recommended.

(c) Drug interactions Cancer patients frequently receive polypharmacy and OCPs have many known drug interactions. Use of antibiotics is a category 1 condition in the WHO recommendations, with no restrictions for OCPs, except for rifampicin and rifabutin. Antacids (magnesium and aluminium types) block absorption of OCPs, and should be avoided for at least 3 h after ingesting the pills. Many analgesics, anticonvulsants and antifungals interfere with microsomal enzymes, thereby reducing the efficacy of OCPs. Equally, OCPs may decrease the clearance of benzodiazepines, tricyclic antidepressants, prednisolone, cyclosporin, and other medications. Hence, use of OCPs in these patients requires careful monitoring [13,20].

OCPs should be avoided in patients with allogenic bone marrow transplant for whom prednisolone and cyclosporins are necessary to prevent graft-versus-host disease and graft reject.

(d) Thrombosis OCPs are contraindicated in women with deep vein thrombosis or pulmonary embolism [25]. However, young women with a history of thromboembolic events related to known foreign bodies (such as central lines) that have been removed are able to take OCPs [20].

In summary, prescription and use of OCPs in teenagers and young adults with cancer should be discussed and assessed on an individual basis, with careful evaluation of specific issues of relevance to them.

2.3.1.2. Progestin-only pills. The Progestin-only pills (POP) (mini-pill) contains no oestrogen, and works through secondary contraceptive methods (thick and less penetrable cervical mucus, endometrial involution, and tubal motility changes) without reliable ovulation inhibition. It is an acceptable contraceptive option for teenagers if oestrogen is contraindicated or not tolerated. It is associated with an increased failure rate, may induce breakthrough bleeding and requires rigorous compliance with dependence on users to take the pill on a rigid schedule (with need for a back-up method if the pill-taking is more than 3 h late). It should be avoided in patients with a history of ectopic pregnancy or who are poorly compliant, or taking rifampicin, griseofulvin and certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine). Progestogen-only pills raise the same issues in patients undergoing chemotherapy as those already listed for OCPs [2,13,20,27].

The progestogens used on a continuous basis to suppress the uterine endometrium are generally not approved for contraceptive purposes. However, they may be prescribed to avoid breakthrough bleeding in teenagers and young adults undergoing chemotherapy for haematological malignancies (for example norethisterone daily during all of the treatment course). In such cases, contraception is a welcome ''secondary'' benefit, but it should be made explicitly clear to the adolescent that contraceptive efficacy cannot be guaranteed and that an effective method should be used if required.

Consequently, progestin-only pill should not be recommended as a first choice contraceptive method for teenagers and young adults undergoing chemotherapy.

2.3.1.3. Emergency contraception. Hormonal emergency contraception (EC), also called the ''morning-after pill'', has been available for over 20 years and is a useful backup method when the usual contraceptive methods fail or unplanned and unprotected sexual activity takes place [20,28]. Different drug regimens are available: (1) the Yuzpe regimen, consisting of 200 μg ethinyloestradiol and 1 mg levonorgestrel, given in two separate doses 12 h apart, with the first dose within 72 h of unprotected course, and (2) the levonorgestrel-only EC (two tablets of levonorgestrel 750 g, administered 12 h apart within 72 h of unprotected intercourse). The WHO trial established levonorgestrel-only EC as the 'gold standard' in hormonal emergency contraception [29], and more than 80 countries have now approved this regimen. A more recent WHO trial showed that a single dose (1.5 mg levonorgestrel) is as effective as the standard two-dose regimen [30]. This would be particularly useful in adolescents and young people undergoing chemotherapy for cancer as it is associated with less side-effects of nausea and vomiting. Levonorgestrel has no medical contraindications, except current ongoing pregnancy [20,31]. Availability of hormonal EC is variable around the world: for example, while in France, the levonorgestrel-only EC is available for sale for women aged less than 18 years at pharmacies, and can be given by nurses freely in schools, in the UK, it is available for sale for women aged 16 years or older at pharmacies. In Switzerland, the Yuzpe regimen is the only hormonal registered EC [2,21,28].

Since adolescents and young adults with cancer run the same risk of unplanned and unwanted pregnancy as healthy ones, discussion of EC should be part of counselling to increase awareness of this method.

The copper intrauterine device (IUD) is a highly effective form of EC with treatment failure rates of less than 1%. It can be inserted up to 5 days after the earliest estimated date of ovulation (i.e., up to day 19 in a woman with a 28-day cycle). IUD insertion is an invasive procedure, which may not be acceptable to adolescents or young women. *The high risk of STIs in this age group, as well as the risk of thrombocytopenia and neutropenia in*

teenage patients undergoing treatment for cancer, renders it unsuitable as an emergency contraceptive method.

2.4. Injectable contraceptives: Depo-Provera

Depot medroxyprogesterone acetate (DMPA, Depo-Provera®) is the most widely used injectable method, is very effective, reversible and does not interfere with sexual intercourse. It provides contraceptive efficacy for 12 weeks without the need for daily compliance. When given at a dose of 150 mg by deep intramuscular injection every 12 weeks, studies have shown failure rates ranging from 0 to 0.7 pregnancies per 100 women years [32]. Its mechanisms of action include persistent suppression of ovulation and ovarian production of oestradiol, through inhibition of the secretion of gonadotrophins, as well as alteration of the yield, composition and physical characteristics of cervical mucus. It induces the formation of a thin and quiescent endometrium with decreased glandular activity. These effects are collectively responsible for the high level of clinical efficacy. The most common side effect is menstrual irregularities, and most users eventually become amenorrhoeic. Amenorrhoea occurs in 8% women after their first injection and in 45% during 10 to 12 months of use [33]. However, despite its efficacy and acceptability, the use of Depo-Provera raises two major concerns in teenage girls and young women with cancer. Firstly, in patients undergoing chemotherapy with the potential for thrombocytopenia and neutropenia, a deep intramuscular injection in the deltoid or the gluteal muscle may be a source of haematoma formation and/or infection. The other area of concern is the potential decrease of bone density with prolonged use of DMPA [34–37]. Adolescence is a crucial time for bone growth, with bone mass accumulating rapidly, with most of the bone mass in the spine and hip being accumulated by the age of 18 years [38]. It has been recommended that DMPA should be avoided in teenagers at risk for osteoporosis such as those with chronic renal failure [13]. Furthermore, it has been shown that children and adolescents undergoing chemotherapy have an increased risk of bone mineral density loss [39,40]. Lastly, DMPA offers no protection against STIs and HIV transmission.

It would therefore seem prudent to avoid the use of Depo-Provera® *in adolescent girls undergoing chemotherapy*.

2.5. Implant contraceptives: Norplant®, Jadelle® (levonorgestrel), Implanon® (etonegestrel)

Norplant I® was the first implantable contraceptive for women to be developed. It is made of six silastic rods containing levonorgestrel, and provides effective contraception for 5 years. The Jadelle® implant (Norplant II) consists of two silastic rods containing levonorgestrel. Whilst it is approved for 5 years of use in other parts of the world, it is licensed for only 3 years in the United States. Implanon® is made of one rod of vinyl ethylene acetate polymer with etonegestrel and provides effective contraception for 3 years. These implants provide reversible contraception and need to be placed subdermally, usually in the upper arm [41,42]. They do not provide any protection against STIs and HIV transmission. The use of Norplant® is not recommended in patients taking medications enhancing liver metabolism, such as phenytoin, carbamazepine, rifampicin, and barbiturates because of the likely increased risk of pregnancy due to lower blood levels of levonorgestrel [43,44]. Side-effects include irregular menstrual bleeding, amenorrhoea, weight gain, headaches and mood changes. This method is convenient and relatively popular with teenagers in that it sidesteps the issue of compliance, it is reliable (failure rate of 0.2 pregnancies per 100 woman-years) and works for a long time. However, this method creates difficulties for adolescents and young women mostly because of the cost, fear of the subcutaneous insertion and side-effects of menstrual irregularities, acne and weight gain [35,45–47]. Patient satisfaction with Norplant® varies and is most directly related to the quality of pre-insertion counselling. Continuation rates in properly prepared adolescents have been reported to be superior with Norplant® use when compared with OCPs [48,49]. Little is known regarding the long-term side-effects of Implanon® in teenagers.

For patients undergoing chemotherapy and expecting severe and/or prolonged thrombocytopenia, there is an issue with irregular menstrual bleeding induced by implants. Furthermore, subdermal insertion of a contraceptive device is an invasive procedure contraindicated in potentially thrombocytopenic patients. Data is lacking about the tolerance and potential sepsis in immunocompromised patients.

It is not recommended to initiate the use of contraceptive implants in teenagers and young adults undergoing chemotherapy. The situation might be different for newly diagnosed patients already using an implant and in whom chemotherapy regimen induces a short and moderate thrombocytopenia. In such cases, removal of the implant might not be necessary, especially if such patients choose to use implants because of failure or side-effects of other contraceptive methods.

2.6. Common contraindications to hormonal contraception in teenagers and young adult patients with cancer

The only absolute contraindication for the use of hormonal contraceptives in female cancer patients is the presence or suspicion of breast cancer. The use of oral combined pills, Depo Provera® and progestin subdermal implants falls under category 4 of the WHO medical eligibility criteria [1,25]. Breast cancer is rare, but not

unknown in very young women: 1% of breast carcinomas occur between 20 and 29 years [50], whilst invasive breast cancers accounts for 0.5% in 15–19 years olds and 4.1% in 20–24 year olds of all female cancers in a recent cancer incidence study [5].

Ovarian tumours rank fourth amongst female cancers in the age group between 15 and 24 years, although subtypes change with age: germ-cell tumours are the most frequently occurring among 15–19 years olds whilst "non-germ cell" cancers account for 70% of ovarian tumours amongst 20–24 year olds [5]. Although extensive surgery with bilateral oophorectomy and hysterectomy is part of the strategy for the treatment of ovarian epithelial cancer; conservative unilateral oophorectomy can be discussed in early stage Ia disease as well as for all germ cell tumours in young women where conservation of fertility is desired. Oestrogen (ER) and progestogen receptors (PR) have been described in ovarian epithelial cancer tissue, with 67% of tumours positive for ER and 47% positive for PR. However, data regarding the potential role of receptor status in ovarian cancer as a predictor of activity of hormonal therapy are inconclusive [51]. No evidence exists regarding the effects of OCPs on recurrence rates in women with conservative treatment for ovarian epithelial cancer. However, it is probably safer to use other contraceptive methods than OCP and long-acting progestogens in young women who have undergone conservative surgery for non germ-cell tumours when the hormonal receptor status is unknown.

Although there have been concerns regarding the use of OCPs in melanoma patients, they do not appear to be contraindicated in these patients [52].

3. Intrauterine device

The intrauterine device (IUD), used by millions of women all over the world, is a very effective contraceptive method. Copper IUDs have failure rates of less than one per 100 women years with the levonorgestrel-releasing IUD (Mirena) being slightly more effective [53]. Traditionally, IUDs have not been recommended as first choice contraceptive methods for adolescents [1,13,15,24]. However, a study showed that in parous adolescents, the clinical performance of IUDs was similar or slightly better than other reversible methods of contraception used by adolescents [54]. Undoubtedly, copper IUD use is associated with an increased incidence of dysmenorrhoea and menorrhagia as well as pelvic inflammatory disease in women exposed to sexually transmitted pathogens. Adolescent girls often participate in "serial monogamy", or have multiple partners, putting them at increased risk of STIs. The presence of cervical ectropion, common during adolescence, also predisposes teenage girls to the acquisition of STIs [24].

Given adequate and appropriate counselling, STI screening and medical care, the copper IUDs can provide effective long-term contraception for adolescents. However, the risk of neutropenia and thrombocytopenia in adolescent cancer patients undergoing chemotherapy, strongly suggests this method should be avoided.

4. Barrier methods

4.1. Female barrier methods (diaphragm, cervical/vault cap, vaginal contraceptive sponge, female condom, vaginal spermicides)

4.1.1. Diaphragms and cervical caps

Diaphragms are shallow, flexible thin latex rubber hemispheres reinforced by a flexible flat or coiled metal spring, available in a variety of sizes, which are placed high in the vagina to cover the cervix. They are used with spermicidal jelly or cream, can be inserted at any time convenient before sexual intercourse and must be left in place for at least 6 h after intercourse. Additional spermicidal jelly or cream must be inserted if intercourse takes place more than three hours after insertion of the device and for each repeat coital act. Contraceptive failure rates range from 12% to over 38% [55]. They require proper fitting by a knowledgeable health professional, who must initially perform a pelvic examination to fit the device, a situation not many adolescents would be willing to tolerate. Besides, many adolescents may be unwilling or unable to deal intimately with their own bodies or prepare so carefully for each act of sexual intercourse [13]. Of notable importance (although without an evidence base), in these patients is the need for a change in size of the diaphragm if there is a change of more than 3 kg in weight. However, for highly motivated adolescents with cancer, this can be an effective method.

The cervical cap is a thimble-shaped dome of rubber that is used with spermicides and applied over the cervix. Cervical cap also needs proper fitting by clinicians, and fitting the cap to the cervix is more difficult than fitting a diaphragm. It can be inserted immediately before or up to 30 min before intercourse, must remain in place at least 8 h before removal, but may be left in place for up to 48 h. Subsequent coital acts require additional spermicidal jelly or pessary to be added to the vaginal side of the cap. Its insertion and removal tends to be more difficult than for the diaphragm, while failure rates are similar [1,13,15].

Cervical cap and diaphragm usage increases the risk of toxic shock syndrome, urinary tract infection, bacterial vaginosis and vaginal candidiasis. They reduce STIs in varying ranges (50–100% for trichomonas, gonorrhoea and Chlamydia), but their role in preventing HIV infection is not clear [56].

4.1.2. Vaginal sponge

This is a sustained-release spermicidal system which absorbs semen and prohibits entrance of sperm through the cervical os. It is generally available over the counter, can be inserted anytime up to 24 h before intercourse, and has a contraceptive action lasting 24 h. Some studies indicate that sponges are less effective than condoms or diaphragms [22,57]. While in nulliparous women, the first-year failure rate may be similar to that of the diaphragm, a study showed that failure rates were higher in parous women [58]. As for diaphragm and cervical caps, adolescents need to be given detailed instructions on sponge use. Development of toxic shock syndrome is not a concern as the nonoxynol-9 contained in the sponge is known to reduce staphylococcal replication and toxin production. While sponges may reduce STI, concern has been expressed about the possibility of enhancing HIV transmission because of vaginal mucosal injury [59].

4.1.3. Female condom

This is a polyurethane soft sheath which is fitted into the vagina before coitus. It is pre-lubricated on its inside with silicone, has two rings, the internal one at the closed end which covers the cervix and the external one at the open end which partially covers the perineum. [60]. Contraceptive failure rates range from 15% to 21%, and tends to result from user failure [61]. Little information is available on its use in adolescence, and its efficacy in preventing STIs [62]. It is also costly, aesthetically displeasing, and associated with a high rate of problems such as misdirection of the penis during intercourse and slippage of the condom [61].

4.1.4. Non-prescription spermicides

Spermicides are valuable adjuncts to the pregnancy and STI-preventive functions of condoms, diaphragms and caps, and do not need to be prescribed by a health professional. They are widely available (foam, cream, jelly, film, suppository or tablet) and may be used alone or with diaphragms, cervical caps, sponges or condoms. Typical failure rates in the first year of use range between 21% and 30% [63,64]. They have to be inserted 10–30 min before intercourse, and reliable protection lasts 1 h. However, leakage from the vagina is inevitable and this common problem of ''messiness'' described by users as well as vulval, penile or vaginal irritation resulting from the detergent action on cell membranes makes their use less acceptable.

Female barriers methods have not received a widespread acceptance by adolescents: they are coital-related methods which interfere with the spontaneity of sex, and teenagers describe preparation and insertion as messy and inconvenient. Used alone, they have a questionable efficacy in the prevention of STIs and cannot be relied upon as an effective method of birth control. Furthermore, concerns about the increased risk of toxic shock syndrome, urinary tract infection, lower genital tract infection and the high failure rate suggest that they should not be recommended in potentially immunosuppressed teenagers and young adults with cancer.

4.2. Male barrier methods (condoms)

Male condoms are non-prescription, single-use contraceptives that serve as mechanical barrier to sperm, bacteria and viruses. Modern condoms are made of latex, and in the 1990s polyurethane condoms were introduced for latex sensitivity or allergy. For the user, it decreases infection acquired through exposure to viral and bacterial agents from cervical, vaginal, vulval or rectal secretions or lesions. For partners of condom users, contact with seminal fluid, infectious urethral discharge or penile shaft or glans penis infectious lesions are prevented. However, transmission of infectious agents from lesions on the areas of the skin not covered by the male condom is still possible, although latex condoms have been shown to prevent the transmission of a whole range of pathogens [65]. Improved education about condoms and fear of STIs, especially HIV, has led to an increased utilisation of condoms by teenagers and young adults over the past decade. Condom failure may result from incorrect use, with the consequence in condom slippage or breakage. Breakage rates during vaginal intercourse in developed countries range from 0% to 6.7% [66]. Condoms do not require parental or healthcare professional involvement and allow confidentiality for adolescents. They are readily accessible (from shops or from a machine), cost-effective, and portable, and allow male participation in contraceptive planning. However, for maximum efficacy, adolescents need to be instructed in the correct and consistent use of condoms.

There is no medical contraindication to the use of male condoms. They prevent STIs and potential HPV transmission, avoid contact with seminal fluid and vaginal secretions, and are effective if properly used (±spermicides). They may be recommended for use by teenagers and young adults with cancer after adequate instructions in their use.

4.3. Advantages of barrier methods

4.3.1. Avoiding exposure to cytotoxics in genital secretions

During chemotherapy, one might expect cytotoxic drugs to be excreted in vaginal secretions or seminal fluid of the patient. In rats, cyclophosphamide penetrates the male reproductive tract and can be transmitted to the female partner and affect progeny [67]. The occurrence of vulvovaginitis has been reported in the wife of a patient with Hodgkin's disease and treated with vinblastine, occurring if sexual intercourse happened

during the first three or four days after the patient recieved vinblastine, and prevented by the use of condom [68]. We are not aware of any studies of levels of cytotoxic drugs in human prostatic secretions, seminal fluid, or vaginal secretions. However, considering these two reports, the use of barrier methods, especially male condoms, need to be discussed before commencement of cytotoxic treatment to avoid contact with seminal fluid or vaginal secretion.

4.3.2. Preventing transmission of sexually transmitted diseases

The occurrence of rapidly changing relationships amongst adolescents, the high probability of multiple sequential sexual partners, and to some extent their greater physiological susceptibility leads to an increased risk of acquiring STIs. Occurrence of bacterial STIs can have serious implications in potentially neutropenic patients.

The most common STI in young women is HPV infection, with a prevalence of ≈30–50% in sexually active young women [69]. These infections are more likely to be transient than in older females, although adolescents who have persistent infection with ''high-risk'' HPV types have an increased risk of developing high-grade squamous intraepithelial neoplasia (SIL) [69–71]. HPV-infection may be asymptomatic, or have a wide clinical spectrum from benign to pre-cancerous lesions. The clinical sequelae of HPV-infection are linked with the type of HPV. Low-risk types are usually associated with anogenital condylomata and high-risk types with low-grade or high grade intraepithelial neoplastic lesions and invasive anogenital cancers. Adolescents are more vulnerable biologically to HPV infections, with postulated mechanisms including inadequate production of cervical mucus, relatively large area of cervical ectopy, increased sensitivity to minor traumas during sexual intercourse, incompletely developed immune response [69].

While HPV infection is clearly associated with the development of cervical cancers, the natural history and course of this infection still remains unclear. Cell-mediated immunity plays a central role in HPV-infection control, and chronic immunosuppression, particularly in renal-transplant and HIV-infection, is a risk factor for development and progression of SILs with these groups having a higher prevalence of cervical HPV infections, SILs and HPV related-cancers. This is thought to be due to prolonged persistence of virus due to impaired clearance of the immune system [72–74]. There is far less data regarding other immunocompromised populations, especially patients with haematological or solid malignancies. One retrospective study has reviewed the cervical cytology of 76 women who underwent bone-marrow transplant (BMT) in two transplant centres and had cervical smears. In bone-marrow transplant patients, the rate of cytological abnormalities was higher than in the general population before and after BMT. Allergenic recipients had a higher rate of cytological abnormalities than autologous transplant-patients, as well as a higher rate of cytological abnormalities post-BMT compared with pre-BMT. These observations suggested that pre-treatment disease, treatment factors and transplant-related factors such as the conditioning regimen and type of transplant may increase the risk of cytological abnormalities [75]. However, we are not aware of any data about the rate of cervical cytological abnormalities following other types of chemotherapy-induced immunosuppression. Radiotherapy or malignancy itself may increase the risk of cervical cytological abnormalities.

Adolescents with malignancy undergoing immunosuppressive treatment may be a very high-risk population for cytological abnormalities and HPV-induced cancers. There are no specific guidelines for cervical cytology screening in this population. Annual Papanicolaou (Pap) smears may be appropriate if they are sexually active. Prospective studies are required to evaluate the rate of cytological abnormalities and HPV shedding in adolescent cancer patients and survivors.

Male condom use has to be promoted in teenagers undergoing chemotherapy, as it is the most protective method against bacterial and viral pathogens, and the only protection against HIV. The dilemma associated with the condom is its poorer rate of contraceptive efficacy compared with other methods. Ideally, to protect these patients against pregnancy and STIs, dual protection would be the best option, i.e., condom plus another method with a lower failure rate for pregnancy. An alternative approach would be condom use with the ability to use emergency contraception in the event of a condom accident [1].

5. Education and information for staff and patients

Fertility is a major concern of teenagers with cancer, as well as teenage survivors of childhood cancer and their families. It is now openly discussed between patients, families, oncology teams and assisted-conception units. However, the prevalence of infertility is far less than 50% in cancer survivors, whilst teenage pregnancy is a not unusual problem, especially in the United States [7,24]. Most of the time, adolescent patients and their families do get the ''risk of infertility'' message provided by the health providers. However they are not aware that, if the teenager is sexually active, he/she is more likely to need protection against pregnancy, as well as against STIs. Furthermore, adolescent cancer patients may not take note of the sexual education provided by the school, community centres, or any other sources, due to the belief that they do not need it.

We recently performed a brief questionnaire survey (Table 2) of 21 teenage cancer units or paediatric oncology units in the UK. Of the 15 respondents (71%), none had a policy regarding contraception issues for their potentially sexually active teenage patients. Hence, whilst fertility impairment is highly likely to be discussed, issues surrounding contraception are less likely to be discussed.

A multitude of medical and psychosocial factors have to be taken into consideration when choosing a contraceptive method for a teenager or young adult cancer patient during or following cancer treatment. Each decision has to be made on an individual basis, in partnership with the teenager. It may be difficult to provide these patients with comprehensive written information through a specific leaflet.

How practice can be improved to share the information about sexual health and contraceptive issues with these patients is a pertinent and very important topic. No literature is available on this specific topic in this population, and it should be noted that the organisation of healthcare and the Family Planning services vary from country to country with different socio-cultural backgrounds. Nevertheless, some suggestions can be made:

- Provision of adequate and relevant information on specific issues to the staff taking care of these patients.
- Establishment of close working relationships with in a multidisciplinary setting between Adolescent Oncology and Family Planning Services staff.
- Provision of practical information about Family Planning Clinics (address, timetables, phone number, website if available, etc.), as well as the leaflets used in Family Planning Clinics about contraceptive methods, sexual health, STIs, available in the adolescent oncology units and out-patients clinics. This can be difficult and has to be discussed in an environment, where the units and clinics are shared by children and adolescents, and where parents of young adolescents can be reluctant to discuss such topics in openly.
- These issues need to be kept in mind when dealing with adolescents who need to be made aware of the staffs' willingness to discuss the issues with them, whilst respecting their need for confidentiality. Inclusion of parents/guardians in such discussions has to be determined on an individual basis in conjunction with the adolescent. It may be pertinent to remind staff that in many countries, contraception can be given to young persons under 18 years of age without parents/guardians being informed.

Table 2
Questionnaire

1. Do you have a policy about contraception and birth control counselling in teenagers and young adults under chemotherapy?		
In males	Yes	No
In female	Yes	No
2. Do you have written information about contraception and chemotherapy?	Yes	No
If yes, would you be happy to share it with us by sending it by post or e-mail?		
3. Do you have any particular remarks/thoughts about contraception in cancer teenagers and young people?		

Contraception guidance may need to be provided at different times of the patient's cancer journey. Even if there is no need for effective contraception at the time of diagnosis, this may change as the situation improves or after treatment. Adolescent cancer patients may become sexually active in the months following completion of therapies, and professionals have to be aware of these changes in the follow-up clinics. An additional problem may be determining the duration of medical contraindication of pregnancy. This decision depends mainly on the cancer prognosis and the risk of relapse. It is an individual decision to be discussed with the patient when a pregnancy is desired. No specific guidelines are available [11].

6. Conclusions

Multiple issues must be considered when choosing a contraceptive method for a teenage or young adult cancer patient. Table 3 summarises the advantages and disadvantages of each method in these patients. Decisions should be made on the basis of the age of the patient, disease, type of treatment, and specific requirements of the individual. Along with respect of confidentiality and a non-judgemental approach, the cornerstones of the process should include education about sexual health, STIs and pregnancy prevention.

Use of the male condom is strongly recommended as it is the best protection against viral (especially HPV) and bacterial pathogens, the only protection against HIV and a protection against seminal and vaginal secretions which potentially contain cytotoxic drugs. A dual method with the condom plus another method with better contraceptive effects would be ideal and has to be discussed whenever medically possible.

Contraceptive issues need to be highlighted with teenage and young adult patients with cancer. This demands the awareness and education of the oncology teams, and collaboration with family planning units.

Conflict of Interest Statement

None declared.

Table 3
Advantages/disadvantages, and recommendations of the different contraceptive methods in teenagers and young adults with cancer

Methods	Advantages	Disadvantages	Recommendations
No method	Convenient, free	No STIs/HIV prevention No pregnancy prevention	Not to be recommended
Abstinence	Best form of pregnancy and STIs prevention, free, no medical CI	Patients with life-threatening conditions not willing to miss a sexual life	Difficult to recommend
Withdrawal	Free, convenient	No STIs/HIV prevention High failure rates	Not to be recommended
Periodic abstinence	Free	No STIs/HIV prevention Inadequate during adolescence	Not to be recommended
OCPs	Low failure rates	No STIs/HIV prevention	To be discussed on individual basis
	Most used contraceptive method in teenagers Involving physician and education	Poor compliance in teenagers girls Issues of thrombocytopenia, nausea/vomiting, mucositis, drug interactions	Ideally combined with male condoms
	No breakthrough bleeding if continuous in potentially thrombocytopenic patients		
Progestin-only pill	Suitable if oestrogen CI	Same issues as for OCP Needs rigorous compliance Increased failure rates	Not to be recommended
Hormonal emergency contraception (morning-after pill)	Post coital method Solution if unprotected or unwanted intercourse	No STIs/HIV prevention	To be discussed as part of the counselling
		Cost Not same easy access in every country	
Injectable contraceptives (Depo-Provera®)	Highly effective	No STIs/HIV prevention	Not to be recommended if undergoing chemotherapy
	No problems of compliance	Intramuscular injection in potentially thrombocytopenic and neutropenic patients Decrease in bone mineral density	
Subdermal implants	Highly effective	No STIs/HIV prevention Irregular bleedings in potentially thrombocytopenic patients	Not to be recommended if undergoing chemotherapy
	Long lasting (3–5 years), reversible	Insertion and foreign body in immunocompromised patients	To discuss removal or not if already inserted at time of diagnosis
	No problems of compliance		
Intra-uterine device	Very effective	No STIs/HIV prevention Unsuitable for adolescents girls Unsuitable for thrombocytopenic and immunocompromised patients	Not to be recommended
Female barrier methods	No medical CI Spermicides/sponges/ Female condoms easily available	STIs/HIV prevention uncertain High failures rates Teenagers not prepared to deal so intimately with their own bodies	Not to be recommended
Male condom	Easily available	Poorer rate of contraceptive efficacy in teenagers	
Recommended ± spermicides			
	No medical CI		Ideally, dual method (condom + another method)
	STIs/HIV prevention Protection against exposure to seminal/vaginal secretions		

Abbreviations: CI, contraindication; OCP, oral combined pill; STIs, sexually transmitted infections.

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References

1. Cullins VE, Huggins GR. Adolescent contraception and abortion. In Koehler-Carpenter SE, Rock JA, eds. *Pediatric and Adolescent Oncology*. Philadelphia, Lippincott, Williams and Wilkins, 2000. pp. 364–392.
2. Alvin P. Adolescents and contraception. What should the pediatrician know? (Part one). *Arch Pediatr* 2001, **8**, 1251–1259., Review.
3. Wellings K, Nanchahal K, Macdowall W, *et al*. Sexual behaviour in Britain: early heterosexual experience. *Lancet* 2001, **358**, 1843–1850.
4. Smith MA, Gloecler-Ries LA. Childhood cancer: incidence, survival and mortality. In Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. Philadelphia, Lippincot, Williams and Wilkins, 2002. pp. 1–12.
5. Wu XC, Chen VW, Steele B, *et al*. Cancer incidence in adolescents and young adults in the United States, 1992–1997. *J Adolesc Health* 2003, **32**, 405–415.
6. Bleyer WA. The impact of childhood cancer on the United States and the world. *CA Cancer J Clin* 1990, **40**, 355–367.
7. Byrne J, Mulvihill JJ, Myers MH, *et al*. Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. *N Engl J Med* 1987, **317**, 1315–1321.
8. Blum RW. Sexual health contraceptive needs of adolescents with chronic conditions. *Arch Pediatr Adolesc Med* 1997, **151**, 290–297.
9. Coupey SM, Alderman EM. Sexual behavior and related health care for adolescents with chronic medical illness. *Adolesc Med* 1992, **3**, 317–330.
10. Suris JC, Resnick MD, Cassuto N, *et al*. Sexual behavior of adolescents with chronic disease and disability. *J Adolesc Health* 1996, **19**, 124–131.
11. Gbolade BA. Women with other malignant disease. In Killick S, ed. *Contraception in practice*. London, Martin Dunitz Ltd., 2000. pp. 19–28.
12. Jemmott 3rd JB, Jemmott LS, Fong GT. Abstinence and safer sex HIV risk-reduction interventions for African American adolescents: a randomized controlled trial. *JAMA* 1998, **279**, 1529–1536.
13. Greydanus DE, Patel DR, Rimsza ME. Contraception in the adolescent: an update. *Pediatrics* 2001, **107**, 562–573., Review.
14. Anne Grinyer. Sexuality and fertility: confronting the taboo. In David Clarke, ed. *Cancer in young adults: through parent's eyes*. Buckingham-Philadelphia, Open University Press, 2002. pp. 61–75.
15. Rieder J, Coupey SM. The use of nonhormonal methods of contraception in adolescents. *Pediatr Clin North Am* 1999, **46**, 671–694.
16. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med* 1995, **333**, 1517–1521.
17. Wilcox AJ, Weinberg CR, Baird DD. Post-ovulatory ageing of the human oocyte and embryo failure. *Hum Reprod* 1998, **13**, 394–397.
18. Dunson DB, Baird DD, Wilcox AJ, *et al*. Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation. *Hum Reprod* 1999, **14**, 1835–1839.
19. Wilcox AJ, Dunson D, Baird DD. The timing of the fertile window in the menstrual cycle: day specific estimates f rom a prospective study. *BMJ* 2000, **321**, 1259–1262.
20. Gold MA. Prescribing and managing oral contraceptive pills and emergency contraception for adolescents. *Pediatr Clin North Am* 1999, **46**, 695–718.
21. Contraception in teenagers. *Drug Ther Bull* 2002, **40**, 92–95.
22. Trussell J, Hatcher RA, Cates Jr W, *et al*. Contraceptive failure in the United States: an update. *Stud Fam Plann* 1990, **21**, 51–54.
23. Greydanus DE, Lonchamp D. Contraception in the adolescent. Preparation for the 1990s. *Med Clin North Am* 1990, **74**, 1205–1224., Review.
24. Brooks TL, Shrier LA. An update on contraception for adolescents. *Adolesc Med* 1999, **10**, 211–219., Review.
25. World Health Organization. Improving access to quality care in family planning: Medical eligibility criteria for contraceptive use, 3rd ed., Geneva, Switzerland; 2004.
26. Owens K, Honebrink A. Gynecologic care of medically complicated adolescents. *Pediatr Clin North Am* 1999, **46**, 631–642.
27. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. *Contraception* 1994, **50**(suppl), S1-195.
28. Ottesen S, Narring F, Renteria SC, *et al*. Emergency contraception among teenagers in Switzerland: a cross-sectional survey on the sexuality of 16- to 20-year-olds. *J Adolesc Health* 2002, **31**, 101–110.
29. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task force on postovulatory methods of fertility regulation. *Lancet* 1998, **352**, 428–433.
30. von Hertzen H, Piaggio G, Ding J, *et al*. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002, **360**, 1803–1810.
31. Hewitt G, Cromer B. Update on adolescent contraception. *Obstet Gynecol Clin North Am* 2000, **27**, 43–62., Review.
32. Lande RF. New era for injectables. Population Reports, Series K, No. 5. Baltimore, Johns Hopkins School of Public Health, Population Information Program, August 1995.
33. Belsey EM. Vaginal bleeding patterns among women using one natural and eight hormonal methods of contraception. *Contraception* 1988, **38**, 181–206.
34. Scholes D, Lacroix AZ, Ott SM, *et al*. Bone mineral density in women using depot medroxyprogesterone acetate for contraception. *Obstet Gynecol* 1999, **93**, 233–238.
35. Cromer BA, Blair JM, Mahan JD, *et al*. A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. *J Pediatr* 1996, **129**, 671–676.
36. Harel Z, Cromer B. The use of long-acting contraceptives in adolescents. *Pediatr Clin North Am* 1999, **46**, 719–732., Review.
37. Busen NH, Britt RB, Rianon N. Bone mineral density in a cohort of adolescent women using depot medroxyprogesterone acetate for one to two years. *J Adolesc Health* 2003, **32**, 257–259.
38. Matkovic V, Jelic T, Wardlaw GM, *et al*. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *J Clin Invest* 1994, **93**, 799–808.
39. Leiper AD. Osteoporosis in survivors of childhood malignancy. *Eur J Cancer* 1998, **34**, 770–772.
40. Arikoski P, Komulainen J, Riikonen P, *et al*. Impaired development of bone mineral density during chemotherapy: a prospective analysis of 46 children newly diagnosed with cancer. *J Bone Miner Res* 1999, **14**, 2002–2009.
41. Meirik O. Implantable contraceptives for women. *Contraception* 2002, **65**, 1–2.
42. Glasier A. Implantable contraceptives for women: effectiveness, discontinuation rates, return of fertility, and outcome of pregnancies. *Contraception* 2002, **65**, 29–37., Review.
43. Sivin I. International experience with NORPLANT and NORPLANT-2 contraceptives. *Stud Fam Plann* 1988, **19**, 81–94.

44. Haukkamaa M. Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment. *Contraception* 1986, **33**, 559–565.
45. Berenson AB, Wiemann CM. Use of levonorgestrel implants versus oral contraceptives in adolescence: a case-control study. *Am J Obstet Gynecol* 1995, **172**, 1128–1135.
46. Weisman CS, Plichta SB, Tirado DE, *et al*. Comparison of contraceptive implant adopters and pill users in a family planning clinic in Baltimore. *Fam Plann Perspect* 1993, **25**, 224–226.
47. Ammermann SD. The use of Norplant and Depo Provera in adolescents. *J Adolesc Health* 1995, **16**, 343–346., Review.
48. Zibners A, Cromer BA, Hayes J. Comparison of continuation rates for hormonal contraception among adolescents. *J Pediatr Adolesc Gynecol* 1999, **12**, 90–94.
49. Polaneczky M, Slap G, Forke C, *et al*. The use of levonorgestrel implants (Norplant) for contraception in adolescent mothers. *N Engl J Med* 1994, **331**, 1201–1206.
50. Kothari AS, Beechey-Newman N, D'Arrigo C, *et al*. Breast carcinoma in women age 25 years or less. *Cancer* 2002, **94**, 606–614.
51. Perez-Gracia JL, Carrasco EM. Tamoxifen therapy for ovarian cancer in the adjuvant and advanced settings: systematic review of the literature and implications for future research. *Gynecol Oncol* 2002, **84**, 201–209.
52. Osterlind A, Tucker MA, Stone BJ, *et al*. The Danish case-control study of cutaneous malignant melanoma. III. Hormonal and reproductive factors in women. *Int J Cancer* 1988, **42**, 821–824.
53. Sivin I, Schmidt F. Effectiveness of IUDs: a review. *Contraception* 1987, **36**, 55–84.
54. Diaz J, Pinto Neto AM, Bahamondes L, *et al*. Performance of the copper T200 in parous adolescents: are copper IUDs suitable for these women. *Contraception* 1993, **48**, 23–28.
55. Trussell J, Strickler J, Vaughan B. Contraceptive efficacy of the diaphragm, the sponge and the cervical cap. *Fam Plann Perspect* 1993, **25**, 100–5, 135.
56. Rosenberg MJ, Gollub EL. Commentary: methods women can use that may prevent sexually transmitted disease, including HIV. *Am J Public Health* 1992, **82**, 1473–1478.
57. Edelman DA, McIntyre SL, Harper J. A comparative trial of the Today contraceptive sponge and diaphragm. *Am J Obstet Gynecol* 1984, **150**, 869–876.
58. McIntyre SL, Higgins JE. Parity and use-effectiveness with the contraceptive sponge. *Am J Obstet Gynecol* 1986, **155**, 796–801.
59. Daly CC, Helling-Giese GE, Mati JK, *et al*. Contraceptive methods and the transmission of HIV: implications for family planning. *Genitourin Med* 1994, **70**, 110–117., Review.
60. Soper DE, Brockwell NJ, Dalton HP. Evaluation of the effects of a female condom on the female lower genital tract. *Contraception* 1991, **44**, 21–29.
61. Bounds W, Guillebaud J, Newman GB. Female condom (Femidom). A clinical study of its use effectiveness and patient acceptability. *Br J Fam Plan* 1992, **18**, 36–41.
62. Trussell J, Sturgen K, Strickler J, *et al*. Comparative contraceptive efficacy of the female condom and other barrier methods. *Fam Plann Perspect* 1994, **26**, 66–72., Review.
63. Raymond E, Dominik R. Contraceptive effectiveness of two spermicides: a randomized trial. *Obstet Gynecol* 1999, **93**, 896–903.
64. Fu H, Darroch JE, Haas T, *et al*. Contraceptive failure rates: new estimates from the 1995 National Survey of Family Growth. *Fam Plann Perspect* 1999, **31**, 56–63.
65. Centers for Disease Control. Condoms for prevention of sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep* 1988, **37**, 133–137.
66. Family Health International. How human use affects condom breakage. *Network* 1991, **12**, 10–14.
67. Hales BF, Smith S, Robaire B. Cyclophosphamide in the seminal fluid of treated males: transmission to females by mating and effect on pregnancy outcome. *Toxicol Appl Pharmacol* 1986, **84**, 423–430.
68. Paladine WJ, Cunningham TJ, Donavan MA, *et al*. Possible sensitivity to vinblastine in prostatic or seminal fluid (letter. *N Engl J Med* 1975, **292**, 52.
69. Kahn JA. An update on human papillomavirus infection and Papanicolaou smears in adolescents. *Curr Opin Pediatr* 2001, **13**, 303–309.
70. Moscicki AB. Human papillomavirus infection in adolescents. *Pediatr Clin North Am* 1999, **46**, 783–807., Review.
71. Woodman CB, Collins S, Winter H, *et al*. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001, **357**, 1831–1836.
72. Bouwes Bavinck JN, Berkhout RJ. HPV infections and immunosuppression. *Clin Dermatol* 1997, **15**, 427–437.
73. Volkow P, Rubi S, Lizano M, *et al*. High prevalence of oncogenic human papillomavirus in the genital tract of women with human immunodeficiency virus. *Gynecol Oncol* 2001, **82**, 27–31.
74. Sun XW, Kuhn L, Ellerbrock TV, *et al*. Human papillomavirus infection in women infected with the human immunodeficiency virus. *N Engl J Med* 1997, **337**, 1343–1349.
75. Sasadeusz J, Kelly H, Szer J, *et al*. Abnormal cervical cytology in bone marrow transplant recipients. *Bone Marrow Transplant* 2001, **28**, 393–397.