The role of the gynecologist in enhancing positive adolescent sexuality: integrating prevention into clinical practice

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THE ROLE OF THE GYNECOLOGIST IN ENHANCING POSITIVE ADOLESCENT SEXUALITY: INTEGRATING PREVENTION INTO CLINICAL PRACTICE

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ABSTRACT

One of the key challenges faced by pediatric and adolescent gynecologists is the integration of positive sexuality and prevention into clinical practice. These goals can impact the sexual life and long-term reproductive health of adolescents, however, unfortunately, they are often not achieved. In this thesis, I will discuss how focusing on prevention can be influential and empowering for adolescents and their families, as well as for healthcare providers. I will present topics that reflect my own research and that exemplify the challenges encountered when working at different levels of prevention.

Gynecological aspects of prevention that can impact adolescent sexuality and sexual well-being can be primordial, primary, secondary, or tertiary. In primordial prevention, the use of correct nomenclature for the reproductive organs from early childhood seems to have a positive impact on girls' appreciation of their bodies and their reproductive organs. This subsequently translates into making consensual decisions about intimate contact and choosing the best contraceptive approach in-line with personal needs, preferences and values. In primary prevention, evidence-based knowledge about HPV vaccination can help to dispel myths and address concerns, potentially leading to higher vaccination rates and better population protection. Primary prevention may also be achieved through optimizing the choice of contraception for preventing unwanted pregnancies, and healthcare providers can assist adolescent individuals to determine their own reproductive health needs, resulting in enhanced effectiveness, satisfaction, and continuation rates.

In secondary prevention, increasing awareness of sexually transmitted diseases among adolescents and healthcare providers may reduce their burden through earlier detection and lower transmission rates. Facilitated, affordable access to healthcare providers and testing is critical in preventing the long-term reproductive repercussions of sexually transmitted infections, especially in a high-risk population such as sexually-active adolescents. In tertiary prevention, the challenges are multiple, and a key example of this is polycystic ovary syndrome. Tertiary prevention challenges in this condition include early diagnosis and rapid initiation of preventive measures such as, weight control and physical activity to avoid metabolic syndrome, cardiovascular risk, and manage anxiety and/or depression, which can result in a diminished quality of life and sexual life.

In this thesis, I will describe how prevention at all levels can be readily incorporated into pediatric and adolescent gynecological clinical encounters. Prevention can be achieved through encouraging self-esteem, including positive sexuality, whether in screening or during the management of different conditions. I will also reflect on the role of an academic clinical educator in pediatric and adolescent gynecology in supporting prevention and positive sexuality, and the impact of a dedicated pediatric and adolescent unit in a university hospital.

TABLE OF CONTENT

ABBREVIATIONS

PAG	Paediatric and adolescent gynaecologist
HCP	Healthcare providers
HPV	Human papillomavirus
STI	Sexually transmitted infections
SARC	Short-acting reversible contraception
LARC	Long-acting reversible contraception
IUD	Intrauterine device
PID	Pelvic inflammatory disease
WHO	World Health Organization
MEC	Medical eligibility criteria
CT	Chlamydia trachomatis
NG	Neisseria gonorrhoea
PCR	Polymerase chain reaction
PCOS	Polycystic ovary syndrome
MRI	Magnetic resonance imaging
OCP	Oral Contraceptive pill
HRQoL	Health-related quality of life

INTRODUCTION

In my 15 years of practice as a pediatric and adolescent gynecologist (PAG), I have encountered a diversity of situations that required sexual education. Education of patients, their parents, colleagues (pediatricians and gynecologists), and, sometimes, other members of the general public. Education is the cornerstone of preventative medicine and, as such, is a vital component of the role of the PAG.

Adolescence is a pivotal phase in the life of an individual where biological changes, environmental factors (socioeconomic and cultural), and changes in social interactions with peers and adults (family, school and community) come into play. Home (parents and siblings), school (peers and teachers), and various social settings, along with the internet and media, are key sources of information on sexuality for adolescents, but also on beliefs and values that will define an adolescent's personal choices later in life[1].

Too many adolescents are sexually illiterate[2]. Healthcare providers (HCP) must address many gaps in information, misconceptions, and myths in relation to sexual health and well-being. This task seems overwhelming and time-consuming for many providers and, in particular, for trainees. Nevertheless, changing misconceptions is crucial for enabling adolescents and their parents to evolve in a positive and healthy way. Fortunately, most adolescents are eager to learn, to be informed and "relevant", and we as physicians must help them to achieve this learning[3].

When it comes to sexuality, communication is far from optimal, both in the homes of the adolescents and between peers, but also in medical consultations. Parents often do not discuss sexual issues with their children, and they underestimate the impact they could have on their child's decisions on how and when to have sex. HCPs are often reluctant to bring up the subject for fear of providing tacit permission to explore sexual behaviors. The HCP can often feel embarrassed discussing sensitive subjects such as masturbation and/or sexual activity because of a belief that intimate questions are intrusive. In reality, sexual education and provider/parent communication about sexuality are associated with delayed sexual activity and more consistent use of contraception[2]. Thus, overlooking adolescent sexuality

could have a negative impact to their overall health[3]. Although most adolescents trust their physician to keep a secret when it comes to sexual matters[4], HCPs must specifically address confidentiality, thus enabling an open dialogue on the subject[5].

Sexuality is a normal part of life and the development of all human beings. Teaching adolescents their human rights, and making sexuality an integral part of this, reinforces an adolescent's rights to receive information and develop competences necessary for their well-being in a world where sexuality is omnipresent.

As gynecologists, we tend to assume that the young women coming to see us are informed and knowledgeable. They present because they are aware that they need contraception, and perhaps they want to be tested for HIV. Often, this is all they know. Topics like anatomy and physiology of sexual organs, the menstrual cycle, the existence of other sexually-transmitted infections (STIs), the importance of human papillomavirus (HPV) vaccination, romantic relationships, and sexual expectations for themselves and their partners are often not explored, discussed, or understood.

In this thesis, I will reflect on some of the challenges faced by PAGs as they relate to the prevention of negative sexual outcomes in adolescent clinical practice. Prevention interventions are critical in PAG consultations and should be implemented based on the best available evidence.

Overarching aim: prevention

Before exploring gynecological aspects of prevention, it is important to define different levels of prevention. **Primal or primordial prevention** is a relatively new concept referring to all measures designed to prevent the development of risk factors early in life[6,7]. **Primary prevention** stops the disease process or medical condition becoming established by eliminating causes or increasing resistance to causes. **Secondary prevention** interrupts the disease process before it becomes symptomatic. **Tertiary prevention** limits the physical and social consequences of a symptomatic disease or condition[8].

PRIMORDIAL PREVENTION

Knowledge of sexual and reproductive anatomy and physiology

Primordial prevention can start in infancy by using the correct terminology for the reproductive organs, just as other body parts are named in the daily routine of washing and grooming a small child, diaper changes and potty time. In an American study from 2008, it was observed that only 10% of pre-school children knew the correct terms for penis, breast and vulva. This was also the case in a similar report published in 1990 by the same author, illustrating that little progress had been made by parents in teaching the correct terms for the genitals over more than a decade[9]. Using anatomically correct sketches of children and their "private parts" (parts covered by a bathing suit – Figures 1-2), either by HCPs or parents, helps children through repetition and practice to develop a more positive body image, self-confidence, and openness, and a more appropriate representation of these organs[10,11]. In addition, it teaches them about between-gender differences and allows for an introduction to genital functions, which can be empowering[12]. In contrast, the use of euphemisms when describing the genitals could give a child the impression that these organs are embarrassing and shameful. Explaining through images (for example, Figure 3) to children that no-one should ever touch their private parts, except to keep them clean or healthy, helps children to understand the right for privacy and establish boundaries between themselves and others[11-13]. When using the correct anatomical terms in clinical practice, children understand that they can ask questions about these body parts and expect answers that are delivered in a medical and matter-of-fact way. When there are clear rules about privacy, there are no body parts that cannot be discussed.

Another important benefit of using correct terminology is that children are less vulnerable to sexual manipulation and abuse[12]. Children who are comfortable with the right terminology are those whose parents are willing to discuss these topics and those who have probably been warned about abuse. This is likely to deter prospective offenders and have a positive impact on disclosure of abuse[12]. Given the body of evidence demonstrating the negative long-term consequences of sexual abuse on victims, prevention and early intervention are crucial[14].

In conclusion, primordial prevention is essential for laying the foundations for sexual self-esteem and healthy sexuality. HCPs are pivotal in encouraging parents to use proper terminology for the reproductive organs, and assisting in developing a better understanding of genital anatomy and organ functionality.

PRIMARY PREVENTION

Primary prevention could be defined as "health promotion" and "specific protection". While health promotional activities do not treat a specific disease or condition, their objective is to promote health and well-being. Specific protective measures, such as the development of personal hygiene routines, vaccinations, and use of contraception, are all examples of primary prevention[15].

Human papillomavirus vaccine

Epidemiology

Human papillomavirus (HPV) is the most prevalent STI, with most adults contracting the virus at least once in their lifetime[16]. Most HPV infections are asymptomatic and cleared by the host's immune system within 2 years[17], however, they are unlikely to induce antibodies and rarely provide immunological protection against further HPV infection[18]. Despite a growing body of evidence documenting efficiency of the HPV vaccine against genital warts, genital cancer, and anal and oropharyngeal cancers, vaccine coverage in the general population and high-risk groups remains suboptimal. The proportion of total cancer cases attributable to HPV in women and men differs significantly by geographical region and economic development status of the country[19]. Transmission rates differ by gender, with higher female-to-male transmission compared with male-to-female transmission further increasing cancer incidence rates in both male and female partners and necessitating vaccination of both genders[20].

HPV vaccination in adolescents

Media reports, social media, personal experiences and attitudes, and, in particular, the recommendation of HCPs, all have a significant influence on the decision to undergo HPV vaccination. A lack of knowledge about HPV among parents and young adults, as well as, providers' misconceptions can prevent vaccination uptake. Arguments given against

vaccination include a lack of effectiveness (especially in men and if introduced after the first sexual intercourse); a lack of safety; and the perception that HPV vaccination will encourage young people to have unprotected sex at an earlier age.

HPV vaccination is gender neutral as a primary prevention measure: it protects men and women from infection with oncogenic HPV types that lead to dysplasia[21]. In regions where early high vaccine coverage is achieved, a significant reduction of cervical dysplasia and genital warts follows[22,23]. A recent American study including more than 2400 women found that the prevalence of vaccine-containing HPV types decreased by nearly two-thirds in girls and women since the introduction of the quadrivalent vaccine[24]. Clinical trials of the 9-valent HPV vaccine demonstrated >96% efficacy against new persistent cervical infections and cervical intraepithelial lesions type 2 due to the additional 5 HPV types in this vaccine[25]. Even unvaccinated individuals benefit indirectly from the vaccination as a result of herd protection[26]. Vaccination initiated after sexarche has been shown to confer excellent immunity against seronegative species and partial immunity against HPV species already present[27].

Clinical studies and post-marketing surveillance have provided data on the safety of the bivalent and quadrivalent HPV vaccines over a period of nearly 20 years, and the World health organization (WHO) Global Advisory Committee on Vaccine Safety has concluded that vaccination against HPV is extremely safe and no causal link has been established with the appearance of Guillain-Barre syndrome[28]. A recent updated review confirmed safety of the 9-valent vaccine and the vaccines in men[29].

To date, studies have not demonstrated a relationship between the receipt of HPV vaccines and the initiation of sexual activity[30,31] or sexual activity-related outcomes such as pregnancy, STI testing or diagnosis, or contraceptive counseling[32]. A cross-sectional study noted a higher number of lifetime partners among sexually-active girls who had received HPV vaccines compared with unvaccinated sexually-active girls[33]. However, this does not necessarily mean that HPV vaccines encouraged these adolescents to have more sexual partners. It is plausible that the HCP and/or parents of these adolescents anticipated their

greater involvement in sexual activity and were more likely to encourage HPV vaccination for them than for girls who they viewed as less likely to have multiple sexual partners.

HPV vaccination in Switzerland

In 2014, the HPV vaccination rate in Switzerland was about 50%, with large disparities between cantons. More specifically, a higher vaccine coverage was observed among French-speaking compared to Swiss-German-speaking regions. The factors contributing for such a difference in French speaking region are provincial vaccination programs at schools which also include boys and in general higher acceptance for vaccinations, compared to Swiss-German-speaking regions[34]. These regional variations in vaccine uptake diminish the overall effect of vaccination on HPV-16 prevalence in Switzerland, but the effect size is small. Cantonal efforts towards HPV prevalence reduction by increasing vaccination uptake are impaired by cantons with low vaccination uptake[35]. In provinces where HPV vaccination is school-based, the vaccination rate is significantly higher[36].

HCPs who provide vaccine advice are encouraged to deliver evidence-based information on the HPV vaccine and to open an active, non-judgmental dialogue with adolescents and their parents. A stronger recommendation by Swiss HCPs for HPV vaccination is probably required in order to improve uptake and coverage, which, in turn, should lead to a decrease in cancer prevalence.

I participated in the development of a Swiss national guideline for HCPs that provides working tools for addressing issues around HPV vaccination[17]. As part of the process, we identified common barriers and questions about HPV vaccination (such as efficacy, safety, side effects etc.), and developed evidence-based answers delivered in a lay language that can help HCPs introduce a discussion on HPV vaccination during the first medical encounter with an adolescent (Table 1).

In conclusion, suboptimal HPV vaccination rates continue to persist, which will result in preventable deaths of women and men. This is despite international and national guidance, and efforts by learned societies, to achieve vaccination rates that are commensurate with herd health targets. HCP education of parents and adolescents to address unfounded concerns and debunk the myths is key to lowering preventable cancer rates. Enhanced efforts at all levels of healthcare provision to achieve desired HPV vaccination targets is essential to ameliorate HPV-associated morbidity and mortality and to confer the public health benefits that will ensue.

Contraception

The introduction of contraception to sexually-active adolescents is considered as a "specific protection" since it principally prevents them from having an unwanted pregnancy in addition to preventing sexually-transmitted diseases (barrier methods). Teen pregnancy places the adolescent mother at risk of low educational attainment, unemployment, and poverty[37]. Teen mothers are also at an increased risk of adverse pregnancy outcomes including low birth weight, preterm delivery, stillbirth, and preeclampsia, as well as feelings of social isolation, delayed or neglected educational goals, and maternal depression[38,39]. When an adolescent or young woman has access to reliable contraception, pregnancy can be safely delayed, and their education can be completed before entering into motherhood.

Global teenage pregnancy, birth, and abortion rates have steadily declined in recent years, however, more than 80% of pregnancies among teenagers are unwanted and preventable[40]. In Switzerland, rates of adolescent pregnancy and pregnancy termination have been low and stable, with a decline observed in 2017 to 153 deliveries and 690 pregnancy terminations in adolescents <19 years old[41,42]. In 2013, among 15-19-year-olds, there were 26 births and 11 terminations of pregnancy per 1000 adolescents in the United States compared with 2.1 and 3.3, respectively, in Switzerland[41-43]. This low rate of pregnancies could be attributed to school-based sex education programs, reinforced by national AIDS campaigns promoting condom use[44], relatively high use of contraceptives, the availability of over-the-counter emergency contraception, and facilitated access to family planning consultations free of charge and availability of gynecologists.

Preventing teen pregnancy – a core indicator of adolescent health – is a major public health priority, with the aim of providing access to safe and highly effective contraception[45]. The options for reversible contraception available for adolescents has expanded dramatically in the last 20 years, and now includes short- and long-acting contraceptives (SARC and LARC, respectively), as well as emergency contraception.

Why long-acting reversible contraception?

The hormonal and non-hormonal (copper) intrauterine devices (IUDs) and progesterone implants are considered LARCs. They are not user-dependent and, therefore, user error is minimal. LARCs do not require maintenance, such as refills, timing, replacing, or dosing, thus making them highly effective contraceptive methods that are ideal for adolescents.

Typical use of LARCs is at least as effective as many female sterilization methods, yet it is immediately reversible. International societies, such as the American Academy of Pediatricians, American College of Obstetrics and Gynecology, the Centers for Disease Control and Prevention (CDC), and the WHO advocate that LARCs should be presented as first-line contraceptive options for sexually-active adolescents. Despite these recommendations, SARCs (combined oestro-progestative oral contraceptive pill, ring, or patch) continue to be the most common form of contraception used by adolescents, despite a 20-fold higher failure rate[46]. Use of SARCs in under 21-year-olds has also been associated with a failure risk that is two times higher than that observed in older individuals – a situation that is not observed with LARCs[46].

Being the most effective forms of reversible contraception, progesterone-based LARC methods are also approved as a treatment for severe dysmenorrhea, endometriosis, and heavy menstrual bleeding. They can be used to achieve menstrual suppression in adolescents who can benefit from having no or little bleeding, such as those who are confined to a wheelchair or have developmental delays for whom personal hygiene at the time of menses presents a challenge.

How many adolescents are actually using IUDs?

Despite very limited contraindications to their use,[47,48] IUD utilization among adolescents remains low. In the United States, about 3.6% of those aged 15-19 years and 6% of those aged 20-24 years use IUDs as contraception[45]. In France, 6.5% of young women have an IUD[49] and, in 2012 in Switzerland, only 1% of adolescents aged 15-19 years and 3% of young adults aged 20-24 years reported using an IUD according to a national phone survey on contraceptive use[50].

Another recent Swiss survey assessing adolescent sexuality and behavior has shown that, among the 7142 respondents aged 24 to 26 years, 9.3% used an IUD during their last intercourse compared with >50% participants using SARCs[51].

Barriers to IUD use

For many years, the use of IUDs in nulliparous women has been questioned due to issues such as younger age, lack of experience with gynecological examination, and seemingly increased pain perception[52]. The 2013 global survey of healthcare practitioners' beliefs and practices around intrauterine contraceptive method use in nulliparous women evaluated the attitude of health practitioners from 15 countries and concluded that the main concerns about IUD use in nulliparous women were difficulty with insertion and subsequent pelvic inflammatory disease (PID)[53]. Approximately half of the responding physicians were not aware of the WHO's Medical Eligibility Criteria (MEC) recommendations, which state that the advantages of IUD use in nulliparous women generally outweigh the theoretical and proven risks (MEC category 2) for both copper and hormonal IUDs[54].

Provider recommendation, education, and attitudes

In 2014, we conducted an online survey in Switzerland that was completed by 299 gynecologists (17.6% response rate). The most frequently-reported obstacles to IUD prescription to nulliparous women were concerns over painful insertion (57.9%), difficulty with insertion (46.2%), higher risk of perforation (30.5%), and infection (26.4%), which was in-line with the results from the 2013 global survey. Our study also found that only 37.3% of the Swiss gynecologists surveyed had a full knowledge of the MEC 2 category recommendations[55]. Reports of these perceived obstacles were associated with less frequent IUD insertion in nulliparous women[55] (predominantly adolescents) (Figure 4). In contrast, the risk of expulsion was considered significantly lower ($p<0.0001$) in nulliparous compared with multiparous women in our study – a perception that does not concur with the literature.

In 2016, an American review noted that a number of providers across the United States incorrectly identified nulliparous adolescents as ineligible for IUD insertion, expressed concern with safety in the adolescent population, and noted a lack of training and comfort surrounding the application of LARC methods[56].

When HCPs have been asked in studies what could increase their confidence in IUD use in nulliparous women, they mostly wished to have more information in relation to pain during insertion, risk of infection, and expulsion rates[48,57].

Adolescents' attitudes and education

Focus groups have shown that adolescents who choose IUDs do so because of their effectiveness, ("peace of mind"), duration of use ("delay childbearing until after obtaining further education"), and convenience ("low-maintenance")[58]. Copper IUDs are chosen in order to avoid hormones or due to perceived weight gain or side effects experienced previously with other hormonal contraceptives (although these are less common with hormonal IUDs due to lower systemic hormone levels)[58].

Adolescents' lack of awareness, believing that nulliparity and age exclude them from using an IUD, in addition to myths and misconceptions such as infertility, PID, ectopic pregnancy, acne, and bleeding irregularities, can deter adolescents from asking for an IUD[56]. In order to overcome these barriers, adolescents and their parents need education on contraceptive options available, with a focus on the most effective methods. Providers can educate adolescents and their parents on their eligibility for a LARC, dispel myths, discuss advantages and adverse effects, address parental concerns, and offer anticipatory guidance.

In a recent study of attitudes among adolescents attending a family planning clinic, 55% were not aware of the option of an IUD. Those who had heard of IUDs from a HCP were almost three times as likely to be interested in using one[59].

Research shows that the health belief model, based on self-efficacy, perceived threat, and barriers, is an effective tool for understanding the determinants of modern contraceptive behavior and a predictor of effective strategies to prevent unintended pregnancy. The health

belief model posits that self-efficacy for behavior change increases when perceived barriers are low. Therefore, adolescents who complete a program aiming to increase their knowledge of the probability of conception, the negative personal consequences of pregnancy, personal and interpersonal benefits of delayed and/or protected sexual intercourse, combined with decreased misperceptions about abstinence and consistent contraceptive use, will lower perceive barriers to contraception and promote positive sexual health experiences[60].

Cost and confidentiality

Another identified barrier to the use of IUDs has been cost. In Switzerland, none of the contraceptive methods are covered by medical insurance, and the high up-front out-of-pocket costs of the device and its fitting potentially hinder uptake of IUDs by adolescents.

Also in Switzerland, women have a right to choose their own contraceptives, whether legally adult or not. If an adolescent wishes to maintain confidentiality and is legally able to consent, they can choose an IUD without worrying about disclosure to their parents or legal guardian, which is not the case for all countries.

The Contraceptive CHOICE Project showed that when women were counselled about all contraceptive methods in order of effectiveness, and contraception was provided at no cost, high percentages of women, including teenage girls, chose LARC methods (any LARC method, 75%; IUD, 58%; and implant, 17%)[46].

Dispelling myths and misconceptions

Is insertion more painful in young nulliparous women?

Components of the insertion procedure that may cause pain include the application of the tenaculum to the cervix to stabilize the uterus and provide traction for straightening the cervical canal, passing the uterine sound, advancing the inserter tube through the cervix, and irritation of the endometrial cavity when the device is deployed. Cervical pain is mediated by S2 to S4 parasympathetic nerves, and the T10 to L1 sympathetic fibers innervate the uterine fundus. Although multiple factors influence pain perception or pain reporting, including

sociocultural factors, prior gynecological examination, and a history of severe menstrual pain, insertion pain levels appear to be higher in nulliparous women than in parous individuals[61-63]. It is therefore important that quality evidence guides the use of strategies to minimize pain on insertion.

Many researchers have studied ways to reduce pain with IUD insertion, such as the use of smaller IUDs in nulliparous women. In the current market, hormonal and copper IUDs of reduced length and width, which are better suited to a uterine size smaller than 6 cm, have shown promise in pain reduction[64].

Recently, we have completed a retrospective observational study on a new spherical IUD. The IUD was inserted in 207 women of whom 21.3% were <25 years of age. Among the 44 nulliparous recipients, 86.4% reported no pain on insertion, one had severe pain, and three had a vasovagal reaction. This relatively well tolerated fitting procedure for the spherical IUD could have been related to its insertor with an outer diameter of 3.2 mm, which is the thinnest on the market, and the intrauterine diameter of the formed contraceptive copper ball, which is only 15 mm[65].

A 2015 Cochrane review of 33 studies with a total of 5710 women showed that lidocaine 2% gel applied on the cervix or vaginally, misoprostol (either buccally or vaginally), and most non-steroidal anti-inflammatory drugs did not help to reduce pain. In contrast, use of topical lidocaine (lidocaine 4% gel applied to the surface of the cervix, in the cervical canal and into the intrauterine cavity and lidocaine spray 10% sprayed on the cervical surface and into the cervical canal), tramadol, and naproxen had showed some promise. Unfortunately, most of the effectiveness evidence reviewed was of moderate quality and came from single trials[66].

A 2017 randomized controlled trial found that a para-cervical block (10 ml 1% lidocaine injected at the site of tenaculum attachment and at the cervico-vaginal junction at 4 and 8 o'clock) injected 10 minutes before the procedure significantly reduced the reported pain during IUD insertion in adolescents compared with a sham block[62]. While not routinely recommended for all insertions, the para-cervical block may have a role where cervical dilation is required, or where a difficult insertion or removal is anticipated or experienced. Some inserters offer the inhaled short-acting, self-administered premixed anaesthetic

agent, oxygen nitrous oxide and oxygen (MEOPA), for pain relief during insertion of an IUD. MEOPA has anxiolytic, as well as analgesic properties, but no published studies quantify its effect on pain during IUD insertion.

Finally, there is an important inverse relationship between pain and satisfaction. It has been demonstrated that young women who experience higher levels of pain are less satisfied with the IUD insertion procedure, stressing the importance of pain reduction[52]. Highly motivated women report higher satisfaction with the procedure, despite experiencing pain during the IUD fitting[52].

Are young women with an IUD at increased risk of expulsion or uterine perforation compared with older women?

Any increased risk of IUD expulsion, either complete or partial, is of concern, since undetected expulsion can lead to an unintended pregnancy. A recent review (2018) by Foran et al.[61] reported very divergent rates of IUD expulsion: 2.2% to 19.0% in nulliparous women and from 2.4% to 17.4% in parous women[67]. Overall, there is little difference when comparing the proportion of nulliparous vs parous women experiencing an expulsion (OR 1.26; 95% CI 0.72, 2.18); the rate of which appears independent of uterine cavity length[68]. A retrospective study found a total rate of expulsion of 6%, which was identical whatever the parity and age of the women[69]. However, a systemic review (2017) suggests that young women are at increased risk for expulsion of copper IUDs and may be at increased risk for hormonal IUD expulsion compared with older women[70]. Nevertheless, all data were based on studies considered to be at high risk of bias. In our study on the spherical IUD, the expulsion rate was higher among the younger age group compared with the women >25 years of age: 9.0% vs 5.3%, respectively[71].

In terms of uterine perforation, a recent systematic review[70] including more than 94,000 women reported no significant difference in risk of perforation after hormonal or copper IUD insertion in women of different ages.

Are young women with an IUD at increased risk of infection?

One of the biggest obstacles to the use of IUDs in young women is the provider's concern about infection, possibly leading to PID and infertility. Adolescents are at particularly high risk for transmission of STIs because of age-attributable behavioral and biological factors, as well as the reluctance to seek medical attention for their reproductive health concerns. Use of condoms is therefore advised when simultaneously using other contraceptive methods.

Since rates of PID caused by *Chlamydia trachomatis* and *Neisseria gonorrhea* are higher in sexually-active adolescents compared with older women, testing women under 25 years of age before or at the time of IUD insertion is recommended[45,69]. For IUD placement, the presence of an STI or a PID is a contraindication to IUD insertion until the infection is eradicated[54]. However, if an IUD is left in place while the diagnosis of PID is made, there is no evidence to show an increased likelihood of a more severe disease or long-term sequelae[45].

There are several flaws in studies that have examined the risk of infection among IUD users. These include the use of an inappropriate comparison group, lack of randomized controlled studies, the over-diagnosis of PID among IUD users, and not controlling for confounders. The methodological failings in studies of adolescents using IUDs are no exception[61,70]. Nonetheless, available data suggests that IUDs are not associated with a significantly increased risk of PID for women or adolescents in particular. Indeed, a review of the literature, published in 1992 in the *Lancet*, combining the data from twelve WHO randomized studies on IUDs (>20,000 women including >5000 women between 15-24 years of age), showed a rate of PID of 1.6 cases per 1000 women/year of use. There appears to be an increased risk of PID in the first 20 days after insertion (six times the basic risk), which may represent intrauterine inoculation of a pre-existing lower genital tract infection. Subsequent risk, however, is related to the risk of acquiring an STI and not to the presence of the IUD, and remains extremely low (<1%)[72]. Our narrative review of 26 articles on whether IUD is a risk factor for PID revealed that even in women at high risk of STIs and in countries with a high STI prevalence, the overall risk of IUD-related PID is low[73]. The best quality evidence for this lack of association comes from a retrospective cohort study from the Netherlands, which reported PID rates of 0-0.3% in nulliparous women and 0-0.5% in parous women[61].

Additionally, hormonal IUDs seem to have a protective effect with regard to the transmission of STIs, as a result of the thickening of cervical mucus[69].

Are young women more prone to early IUD removal and a shorter continuation rate?

Although expulsion is the main reason for IUD discontinuation, side effects such as change in bleeding patterns (increased volume or duration) or pain, in addition to infection, are common reasons for IUD removal[58,70,74]. Data from several systemic reviews and a Cochrane review show high continuation rates of between 74-86% for women aged 25 years and younger,[75-77] with continuation rates for IUDs generally higher compared with other contraceptive methods[74,75] and comparable to rates observed in older women[78]. Providing counselling about potential side effects has improved adult users' satisfaction with the IUD, and similar advice may work well for adolescents (see Table 2).

Potential strategies to increase IUD use among adolescents

Clinicians have an influence on IUD uptake. When hearing about IUDs from a HCP, participants in one survey were almost three-times more interested in using one[59]. Effectiveness, duration, convenience, and potential bleeding changes are important to young women when choosing an IUD. However, not all adolescents are well prepared for the immediate and future side effects they may experience with the IUD. Providing pre-insertion counselling and anticipatory guidance about short- and long-term side effects and potential treatment for these side effects will lead to higher continuation rates[58].

Greater efforts should be expended to dispel myths while informing young women about the true benefits and risks associated with IUD use. Unfortunately, studies suggest that some of these myths are largely shared by physicians, who overestimate the risks of infection and ectopic pregnancies, and do not recommend IUDs for nulliparous women[49,70,72,73]. I recently led the current update of the informed consent form for IUD insertion from the Swiss Society of Obstetrics and Gynecology (yet to be validated), which is largely used by Swiss gynecologists. In this update, the eligibility of nulliparous women, including adolescents, for IUD use has been emphasized. This is an example of my work that aims to bring evidence-

based information using various tools to both clinicians and their patients[3,69,73] (see Annex 1).

Although from a public health perspective, LARCs provide efficient user-independent contraception, HCPs should be aware that many women are more comfortable using SARCs, and regulating their contraception, albeit with lower effectiveness[79]. It is therefore important that HCPs assist their patients' self-determination when choosing a contraceptive method, which will ultimately result in greater satisfaction and higher continuation rates[52].

In conclusion LARCs are ideal contraceptive options for sexually-active adolescent girls and should be a first-line option for adolescents worldwide. IUDs are safe, effective, user-friendly, well tolerated, and cost-effective. HCPs are an important catalyst to increasing IUD use among teenagers, by expediting same-day insertion when feasible and delivering evidence-based information. This will enable all women to exercise an informed choice to satisfy their reproductive health needs[80].

SECONDARY PREVENTION

Secondary prevention entails "early diagnosis and prompt treatment" to contain the disease, preventing transmission to other individuals or progression to a symptomatic disease. It could also be described as "disability limitation" where potential future complications and disabilities from the disease are prevented[15]. As an example of secondary prevention in adolescence, this review will focus on the prevention of *Chlamydia trachomatis* (CT).

Chlamydia trachomatis

Introduction

CT infection is the most frequently reported bacterial STI and remains highly prevalent, with >2.9 million new cases reported annually in the USA[81]. Young age is a strong predictor of CT infection, with 63% of all chlamydia infections in the USA reported in persons younger than 25 years of age[81]. The majority of CT infections are asymptomatic, so detection of infection often relies on screening and prevention. For example, early diagnosis and prompt treatment of an individual infected with CT would include a course of antibiotics to eradicate the

pathogen and screening and treatment of any current or previous sexual partners or newborns to infected mothers. Disability limitation for CT infections may include follow-up checks for other STI and reinfection, thus reducing the infection's burden and reproductive complications.

Incidence and prevalence in adolescents

In Switzerland, as in Europe and the USA, the number of CT infections has been steadily increasing. The number of reported cases in Switzerland reached over 11,000 in 2018[82]. The highest rates were noted among 19-24 year-olds, with 691 cases per 100,000 population. This number has more than doubled in the last 6 years (Figure 5).

A study conducted in a STI outpatient clinic in the canton of Vaud in Switzerland reported a CT prevalence of 5.9% among women and 3.9% among men[83]. Another Swiss study undertaken by my team[84] analyzed data provided by the bacteriology laboratory of the Geneva University Hospitals (HUG) between 2014 and 2016, comprising more than 30,000 samples tested for CT and *Neisseria gonorrhea* (NG) using real-time polymerase chain reaction (PCR) amplification. The data showed CT positivity rate peaks between 15-24 years for both women (7.4%, 66/830) and men (7.9%, 489/6103), compared with the total cohort of 3.3% (941/28193) and 4.7% (233/4970) in female and male samples, respectively ($p<0.001$). These rates remained stable through 3 years.

Risk factors in adolescents

The probability of CT transmission between heterosexual partners is estimated globally at 55.5% and at 9.5% per sexual intercourse[85]. Multiple complex factors contribute to the high rate of STIs among teens. The mean age of onset of sexual intercourse in Switzerland is 17 years[51]. Early age of coitarche is a significant risk factor for acquiring an STI. Other important factors include multiple and concurrent partners, suboptimal use of barrier methods, frequent change of partners, sex under the influence of alcohol and drugs, sexual transactions, dating violence, and lack of, or poor, parental guidance[86]. Biologically, the larger cervical ectropion may be more susceptible to pathogenic organisms, with possibly lower

immunoglobulin A levels in the cervical secretions[45].

Adolescents often present for care late in the course of their infection, placing them at higher risk for PID complications or infection of more partners. Delays in care may be attributable, at least in part, to concerns about the confidentiality of medical services and/or high costs of care, highlighting the importance of confidential and free health services for adolescents[81,86].

Coinfection

Adolescents infected with CT may be coinfected with NG[86]. Our data from HUG showed coinfection rates of 32.5% and 23.6% among female and male cohorts, respectively, which are comparable to rates reported elsewhere[87].

A similar rate of 30% was recently reported for coinfection with *Mycoplasma genitalium* (MG)[88]. The high incidence rate of MG among women (15-24 years) with multiple STI risk factors indicates its widespread transmission within sexual networks. A recent review by my team has underlined the association of MG with reproductive tract complications. Our review proposed targeted MG screening programs to young high-risk populations (see Figure 8). The risk of acquiring HIV is also increased in inflammatory STIs, notably infection with CT, but also NG, Trichomonas, and the ulcerative diseases, syphilis, herpes simplex infection, chancroid, and lymphogranuloma venereum[86].

Health implications

PID is a sexually acquired, polymicrobial infection involving the upper genital tract and peritoneal surfaces. PID commonly occurs in women <25 years of age, with the most common pathogens implicated being CT, NG and MG (Table 3)[89-92]. Profound long-term sequelae of PID have been reported and include tubal-factor infertility, ectopic pregnancy, chronic pelvic pain, need for hospitalization and/or surgical intervention, and recurrence of disease. The precise incidence and timing of PID among adolescents is difficult to estimate, and the long-term sequelae from an untreated chlamydial infection have not been fully determined, mainly

because most cases are mild or sub-clinical and not all affected adolescents seek medical care. In addition, the diagnosis of PID is not reportable[93].

Some prospective studies suggest that only 15% of untreated CT infections progress to clinically-diagnosed PID[89]. Large studies report an infertility rate of 18% after symptomatic PID of any cause[93]. In contrast, the rate of PID progression in the general, asymptomatic population followed up for longer periods, appears to be low[94]. Interestingly, natural immunity occurs in girls and women with a CT genital tract infection[95], and spontaneous clearance rates of up to 50% have been documented in untreated lower genital tract colonization with CT[96]. If the chlamydia infection is not cleared completely, a persistent infection or reinfection may induce a chronic low-grade immune response that will destroy host cells and damage the cilia lining of the fallopian tubes. This, in turn, will lead to subsequent repair and scarring which will eventually block the tube and enhance adhesion formation in the pelvic-abdominal cavity[94]. A great deal of uncertainty relating CT to reproductive and gynecological morbidity exists and prospective studies are needed.

A recent retrospective population cohort study in Denmark over 20 years in more than half a million women, showed that, in those who had one or more positive tests for chlamydia, the risks of developing a complication (PID, ectopic pregnancy and tubal factor infertility) were at least 30% higher than in those women who tested negative[97]. In practice, this questions the appropriateness of (annual) screening programs for young sexually-active women, as proposed in many national guidelines[98].

Screening

Screening is a population-based intervention, and providing chlamydia screening is not just a matter of funding for the provision of tests. There are internationally-recognized criteria for appraising the appropriateness of a screening program, for determining whether the benefits outweigh the harms, and for deciding whether the benefits can be achieved at a reasonable cost[99]. The two effects sought by screening are the reduction in the prevalence of chlamydia in the population by controlling its transmission and the reduction in the risk of complications. Screening does not only include the diagnostic test, but also the treatment of positive cases, the identification and treatment of partners, a control test to detect and treat possible

reinfections, and the provision of information and counseling. Screening also has potential adverse effects such as increased post-treatment reinfection rate, negative emotional reactions, or relationship breakdown after a positive diagnosis[100].

It is important for chlamydia treatment to be delivered before irreversible damage to the female genital tract ensues. However, it is impossible to predict in which adolescent the CT infection will progress to PID or clear spontaneously. It has therefore been suggested that individuals in high-risk populations (sexually active youth) or settings (where high prevalence is known) should be screened and treated[81,101]. CT screening programs in women have led to reduced PID rates,[89,102] sometimes by half,[103], and the recent literature suggests a continued decline in PID rates in the United States, most probably related to more extensive and widespread screening[81].

The recommended screening procedures for CT is described in Table 4 and these should be applied to sexually-active individuals. Due to the high rate of coinfection with NG and MG, in the presence of a positive test for CT, screening for MG should be systematically performed (see Figure 6 for guidance) in addition to other STIs.

Treatment and surveillance

Although no clear guidelines exists in Switzerland for screening in young adults, treatment protocols are well established (Table 5). Interestingly, antibiotic treatment interferes with development of natural immunity: individuals who are not treated with antibiotics have fewer reinfections than those who are treated with antibiotics[104].

Single-dose antibiotic therapy may be the ideal option in adolescents because a significant number of young women may not fill their prescriptions. Expedited partner treatment, where the infected individuals typically delivers the prescription or treatment to his or her sexual partner,[89,102] although not tested in adolescents, is a reasonable approach to reducing the high reinfection rate among teenagers when it feasible and legal[105].

Repeat testing at 3-6 months after treatment is advised, as reinfection, not treatment failure, contributes to the disproportionately high rate of STIs in adolescents[102,106]. In an individual

<25 years of age, retesting should be offered whenever there is a change of sexual partner.

Prevention

Prevention of STIs, and sequelae, requires public health measures, such as screening populations at risk, as well as all-inclusive sex education, encouragement to use condoms, and the provision of condoms. The Swiss national program on HIV and other STIs has defined a strategy for the prevention, diagnosis, and treatment of communicable diseases. The recommended measures to decrease the long-term sequelae of STIs include structural and behavioral prevention, vaccination plans, and effective screening and treatment programs. The strategy emphasizes the "legitimate and necessary individuality" of early detection and its importance in terms of public health[107]. One of the prerequisites for its implementation is respect for the principle of equal opportunities, including equitable access to diagnosis and treatment. However, the national program on HIV and STIs does not include specific measures for the control of CT, and currently, there is no national screening program. This area remains the responsibility of the cantons despite the recommendation of the Swiss Federal Commission for Sexual Health[108]. Screening for asymptomatic infections is therefore based on the personal responsibility of the population concerned, whose members can turn to voluntary counseling and testing centers and to HCPs who propose screening in a targeted way according to patient history. It therefore seems paradoxical that, in the age group most affected by chlamydia, with a possible subsequent compromise to future reproductive capacity, there is limited access to screening due to cost. Low-cost screening would ensure that chlamydia screening could be delivered at regular intervals to adolescents and young adults by gynecologists and primary care physicians[109].

The current price of a PCR analysis in Switzerland is between 95- 119 CHF, which represents a high barrier to screening programs and to the testing of individuals. The difference in pricing between Switzerland and other European countries is striking. Even when the price is halved, it still represents almost double the cost invoiced in France[109]. Indeed, in its second report, the Swiss Federal Commission for Sexual Health quotes the conclusions of a group of international experts mandated by the Federal Office of Public Health to evaluate the Swiss policy on HIV and STIs. It was noted in 2009 that public health imperatives and prevention

priorities were compromised by the costs and funding of testing that differed substantially from well-established practices in other countries. This group of experts recommended these tests to be free or as cheap as possible. The Swiss Federal Commission for Sexual Health echoes this by saying that a coherent policy to prevent the spread of STIs requires that test costs be exempt from deductible health insurance franchise, as with HPV vaccination[110].

In the Geneva University Hospitals, for example, CT testing is part of a 25CHF "fixed price" paid by adolescents <20 years of age who attend for consultations. This permits out of pocket payment that is reasonable without involving medical insurance companies, thus protecting confidentiality in relation to legal guardians.

When evaluating health economic models, discount rates are highly influential on the cost-effectiveness of screening programs[111]. The lower the discount rates, the more economically favorable is the balance[109]. In fact, the costs associated with PID hospitalizations, chronic pelvic pain, infertility, and ectopic pregnancies, as well as, the negative impact on women's quality of life and the financial consequences in terms of lost productivity, far exceed the cost of screening[112].

In the absence of evidence on the long-term effectiveness of screening programs, Low et al. suggested promoting broad and equitable access to testing and treatment may be the most appropriate medium-term goal[113]. However, the same author published 9 years later a Cochrane review underlining the lack of solid evidence from randomised controlled studies on the effects of screening. In addition, the review emphasized the moderate level of evidence that detection and treatment of CT infection can have positive impact on PID risk reduction on a personal level[100].

The proposal for screening by the caregiver is subject to the approval of the individual to be screened. However, this agreement will depend partly on a perception of being at risk – a risk that may be underestimated by many young people[114].

The need to understand risk illustrates the importance of sexual health education at school and, more importantly by parents and HCPs. Discussions around sexuality, symptoms and signs (vaginal discharge, pelvic pain etc.) that might indicate a dysfunction of the reproductive organs, and the benefits of using condoms, are all essential to knowledge and

empowerment. Knowledge is power. We recently conducted an exploratory study on knowledge of STIs among young adults in Geneva[115] through focus group discussions (N=44 students, 21 female and 23 male), all participants were between the ages of 18-27 years. The discussions revealed a clear lack of basic knowledge concerning STIs, misconceptions about modes of transmission, and an underestimation of risk in relation to STIs, all of which translates into suboptimal protection despite an awareness of a possible negative impact. Participants criticized the structure and content of sexual education classes and they requested better information about STIs and their symptoms.

Similar attitudes were shared by adolescents in an American study in which adolescents attending an emergency room in an urban setting did not perceive themselves to be at risk of an STI. More than half of the adolescents diagnosed with an STI "definitely did not" think they had an STI, and not one individual with an STI thought he or she may be infected[114].

HCPs can play a key role in the education of adolescents by including developmentally-appropriate discussions about sexual matters and healthy relationships in the annual health check visits, after establishing confidentiality. HCPs can also act as a reliable source of information for parents[3].

Future vaccine

A CT vaccine may have some efficacy if it is administered before irreversible damage occurs in the female genital tract. Unfortunately, a therapeutic vaccine, although theoretically possible, is highly unlikely to be developed, since current methodologies detecting the early onset of upper genital tract pathology are still lacking. For CT, cell-mediated and humoral immune responses will likely be required to elicit optimal protection. Experimental work in mice undertaken with vaccines that are single or multivalent recombinant antigen vaccines seems promising. However, before introducing a vaccine that will prevent PID and infertility in humans, evaluation of adjuvants, routes, and delivery systems that are effective and safe are necessary[104].

In conclusion, adolescents are in a unique period of psychosocial and biologic development, placing them at high risk for STI acquisition and transmission. CT is more prevalent among

adolescents and young adults compared to older men and women. Unfortunately, many providers who care for adolescents fail to discuss sexuality, even at health maintenance visits. Primary care visits present opportunities to educate adolescents on sexual health and development, to promote healthy relationships and to discuss prevention of STIs and HIV. A confidential sexual history and affordable STI screening are essential components of routine care for adolescents and young adults, and updated local guidelines should be used to lead prevention, screening, diagnosis, and management of STIs in this age group.

TERTIARY PREVENTION

The goal of **tertiary prevention** is to reduce the impairment caused by symptomatic disease through physical, psychological and social restoration and to optimize the remaining capabilities and functions of the individual[15].

The objectives of tertiary prevention include attenuating physical and/or emotional pain and damage, halting progression and complications of disease, and repairing the health and functions of the individuals affected by disease. For young people with polycystic ovary syndrome (PCOS), early detection will enable earlier intervention that might prevent or lessen somatic or psychological long-term sequelae that could influence their sexual health.

Polycystic ovary syndrome

Prevalence

PCOS, a complex heterogeneous familial disorder that is phenotypically varied, affects 6-20% (depending on the inclusion criteria) of women of childbearing age and is considered to be the most common endocrinopathy. Despite extensive research, the etiology and pathophysiology of PCOS remains elusive[116,117].

Pathophysiology

A key feature of PCOS is androgen excess manifesting as hirsutism and elevated unbound testosterone. Excessive androgen adrenal production may also be found in some PCOS patients. Elevated androgen, in turn, suppresses sex hormone-binding globulin (SHBG), which contributes to the increased free testosterone concentrations[117]. The pathophysiology of PCOS involves complex interactions between genetic and epigenetic changes, primary ovarian abnormalities, neuroendocrine function alterations, and endocrine and metabolic modifiers, such as anti-Müllerian hormone, pancreatic β-cell function, insulin sensitivity, adiposity, and adiponectin levels[116-118].

Diagnosis in adolescents

The diagnosis of PCOS during adolescence is difficult and controversial because most of the pathological features of PCOS, such as clinical and/or biochemical signs of hyperandrogenism, ovulatory disorders, or ovarian polycystic appearance on ultrasound (PCOM), which are considered abnormal in adult women, are physiological during normal puberty. These result from incomplete maturity of the hypothalamic-pituitary-ovarian axis[119,120]. Suggested criteria for the diagnosis of PCOS in adolescence are shown in Table 6.

In order to make a diagnosis of PCOS, the required diagnostic criteria should persist for 2 years beyond menarche, while other causes of hyperandrogenism should be ruled out (e.g., androgen-secreting tumor and Cushing's syndrome).

For adolescents who have features of PCOS but do not meet diagnostic criteria, frequent longitudinal reassessment are advised at, or before, full reproductive maturity, 8 years post-menarche[118,121]. Polycystic ovaries on ultrasound without hyperandrogenism or menstrual irregularities should not be used alone to diagnose adolescent PCOS. An ovarian volume of more than 12 ml is suggestive, rather than follicular count (as in adult women), given most US are transabdominal[117]. In recent years, magnetic resonance imaging (MRI) has been explored to assess ovarian morphology as results are not altered by obesity. However, for the moment, MRI measurements are used only in research, because of their high price and lack of validation[122].

Hyperinsulinemia, insulin resistance, and obesity may be present in adolescents with PCOS, but are not considered to be diagnostic criteria (Table 6).

Long-term sequelae

In addition to the metabolic and endocrine long-term sequelae such as obesity, dyslipidemia, insulin resistance, hyperinsulinemia, and type 2 diabetes mellitus, some studies have suggested that PCOS is associated with an increased prevalence of psychological and behavioral disorders such as low self-esteem, depression, and anxiety[123]. Lifelong care is required to manage PCOS symptoms and to mitigate long-term health complications[124].

Management in adolescents

Once a firm diagnosis is established, which may require watchful waiting for up to 2 years, management of the adolescent with PCOS should begin early in the disease course and cover both management of hyperandrogenism and prevention and treatment of related comorbid conditions, using a multidisciplinary approach. In general, PCOS therapy in adolescents should be targeted at a reduction of the hepato-visceral adiposity that contributes to the pathogenesis of anovulation and fat excess[116].

An holistic management approach may include weight control and physical exercise programs, insulin sensitizers, androgen receptors blockers, hormonal contraceptives, as well as psychological support[117,118]. Even in the absence of a definitive diagnosis, treatment should be symptom oriented[116].

Baseline treatment

Lifestyle interventions should be based on the combination of calorie-restricted diets, behavioral treatment, and exercise. Increasing physical activity from moderate to vigorous (60 minutes of activity/day, including activities that strengthen muscle and bone at least three-times weekly) is effective in reducing androgen levels and the development of metabolic syndrome in normal weight girls[117,118,125,126]. Decreasing sedentary behavior is at least as important as increasing physical activity[127]. Family treatment is an essential component of lifestyle management in PCOS. HCPs should be aware of the increased prevalence of eating disorders and disordered eating among individuals with PCOS. Expedited assessment, referral and treatment, including psychological therapy, are of utmost importance[124].

Local therapy and cosmetics

Many cosmetic methods exist for unwanted hair removal. Evidence-based studies have placed photoepilation as first-line management for localized hirsutism in PCOS; diode and alexandrite lasers are preferred. Topical eflornithine HCl (13.9%) is recommended as an adjuvant to photoepilation in cases of laser-resistant facial hirsutism or as monotherapy in

patients with facial hirsutism where photoepilation is not indicated[117].

Insulin sensitizer - metformin

Metformin is the most widely used insulin sensitizer in the treatment of adolescent PCOS[117]. Metformin has similar effects to lifestyle interventions in terms of decreasing body weight, but is superior in its effects on decreasing androgen concentrations[117]. A recent systematic review and meta-analysis found that 6 months of combined metformin treatment with lifestyle interventions was associated with a lower BMI and improved menstrual regularity compared with lifestyle modification alone[128]. In overweight or obese adolescents with PCOS, metformin has beneficial effects, but only short-term data are available. In non-obese adolescents with PCOS and hyperinsulinemia, metformin improves ovulation and testosterone levels[117]. Metformin, combined with lifestyle interventions, could be considered in adolescents with suspected symptoms of, or confirmed, PCOS. Nonetheless, more studies are needed to evaluate prevention of metabolic syndrome later in life[124].

Anti-androgen

Anti-androgens reduce androgen excess features more than metformin in monotherapy. Spironolactone is the most commonly-used anti-androgen and, when combined with metformin, was found to be superior to metformin alone in improving features of hyperandrogenism[129]. In sexually active adolescents, anti-androgens must be combined with efficient contraception in order to avoid the risk of malformations in the male fetus[117].

Oral contraceptive pills (OCP) and contraception

OCPs containing both estrogen and progesterone components address multiple issues in adolescents with PCOS. First, estrogen, through its liver receptors, will increase SHBG production and decrease hypothalamic LH secretion, both leading to a reduction in free circulating androgens. The progestin will suppress endometrial proliferation, which can cause irregularity of bleeding (with varying quantities from scant to abundant), often with anovulatory cycles. As a result, acne and hirsutism will be reduced and menstrual regularity

restored.

Adolescents with PCOS may also be exposed to spontaneous and unpredictable ovulation, rendering them at risk for unwanted pregnancy. Accordingly, several guidelines propose OCP as a first-line treatment for adolescents with PCOS, with attention to medical eligibility criteria and individual risk[124,130].

Use of progesterone-only contraception (by injection, implant or pill) does not contribute to an increase in SHBG and although it may exert an effect on the endometrium, is less tolerable due to numerous side effects such as spotting, weight gain, bone loss, acne etc. The progesterone intra-uterine system may be an alternative in individuals with PCOS who have a contraindication to the use of estrogen, given high contraceptive efficiency and very little systemic side effects. Nonetheless, high quality studies on contraceptive treatment options in adolescents with PCOS are lacking[117].

Quality of life

In a systematic review performed by my team, we found PCOS to have a significant negative impact on health-related quality of life (HRQoL) in adolescent girls[126]. Weight issues associated with this syndrome – more than its metabolic impact – are associated with psychological challenges such as low self-image and esteem, anxiety and depression, during an already vulnerable period of life. HRQoL in obese adolescent and young adult women with PCOS can be improved with lifestyle modifications (dietary measures and physical activity) and combined oral contraceptives, with or without metformin[126,131-133]. Both weight loss and OCP use result in significant improvements in several physical and mental domains related to quality of life, depressive symptoms, and anxiety disorders, and combined therapies offer further benefits in overweight/obese women with PCOS[132].

Impact on sexuality

PCOS can also have an impact on sexuality. Although there was no difference in the mean age at first sexual intercourse between sexually-active women with PCOS and controls, controls were 2.8-times more likely to already have had sexual intercourse compared to PCOS patients

in one study[134]. Interviews with sexually-active adolescents with PCOS have revealed that the majority of individuals do not believe the condition has an impact on their sexual lives. However, some individuals report that their poor body image and hirsutism could have contributed to their anxiety during their first intercourse or when having a new sexual partner[135].

Several adolescent girls admitted that they had engaged in unprotected sex because they thought PCOS reduces their risk of becoming pregnant. Others stated being afraid of getting pregnant or/and failing to identify their pregnant state because of their irregular menstrual cycles[135]. The above illustrates the importance of HCP education of adolescents with PCOS on issues that could impact their sexual lives.

Patient–healthcare provider relationship

The diagnosis of PCOS provokes diverse emotions in affected adolescents. Some experience negative emotions because they are affected by a condition they were unaware of. For others, a diagnosis means receiving an explanation for the symptoms they had experienced, which translates into a sense of relief and source of hope in finding adequate treatment[135].

Likewise, patients' personal experiences with different healthcare systems and professionals vary widely, and a patient's belief in their HCP is linked to their treatment adherence. Some adolescents complained about the lack of information provided by their physician, the use of inappropriate terminology for their level of comprehension, or a lack of empathy. Others thought it was the physician's lack of knowledge that explained any delay in diagnosis, insensitive management, or poor communication[136].

A number of young women with PCOS believe that their physician was more interested in the clinical symptoms than in the psychological impact of PCOS, thus neglecting this feature of their condition[135].

A good patient–doctor relationship based on trust, active listening, and empathy is particularly important for the adolescent with PCOS. Initiating treatment at the moment of diagnosis can have a positive effect[137] and help to alleviate frustration[135]. The psychological

effects of the syndrome can be profound in some adolescents, and HCPs should address this aspect with their patients and stay active in searching for psychopathologies[138]. The benefits of psychological support are yet to be evaluated precisely, but need to be part of the multidisciplinary approach recommended for all adolescents with PCOS.

In conclusion, despite the difficult and controversial diagnosis of PCOS during adolescence, suspicion of the condition should initiate early management using a multidisciplinary approach. Close surveillance of hyperandrogenism and prevention and treatment of related comorbid conditions could mitigate long-term health sequelae such as metabolic, endocrine and mood disorders, all of which can have an impact on their sexual lives.

CONCLUSIONS

In this thesis, I have discussed how different levels of prevention may be influential and empowering for adolescents.

In *primordial prevention*, physicians' use of correct nomenclature when examining and discussing the reproductive organs in early childhood could encourage parents and educators to do the same. This has many positive impacts as girls learn to accept and appreciate their bodies and their reproductive organs. Later in life, it also enables them to make consensual decisions regarding permission to have an intimate contact or choosing the most appropriate contraceptive for them.

In *primary prevention*, evidence-based knowledge can be translated into the education of parents and adolescents about concerns and myths relating to HPV vaccination. This will favor higher vaccination rates and, consequently, could help reduce HPV-associated morbidity and mortality. Primary prevention is also exemplified in the choice of an efficient contraceptive method to preventing unwanted pregnancies. I focused on LARCs because they are safe, effective, user-friendly, well tolerated, and cost-effective, placing them as a suitable contraceptive option for sexually-active adolescent girls. The assistance of HCPs in clarifying an individual's self-determined reproductive health needs could ultimately result in higher satisfaction and continuation rates.

In *secondary prevention*, increasing awareness of STIs among adolescents and HCPs would also reduce their burden. Disseminating knowledge on STIs can start with any open discussion about sexuality at home, in schools, and during wellness check visits. In addition, facilitated, affordable access to care is key to preventing reproductive long-term repercussions, especially in high-risk populations, such as adolescents.

In *tertiary prevention*, the challenges are multiple for PCOS. First, HCPs should be alert to the presence of menstrual irregularities and hyperandrogenism as early as 2 years post-menarche. Second, they should be prepared to educate an adolescent with PCOS about the importance of taking immediate preventive measures, such as activity increases and weight and mood control to avoid metabolic syndrome, cardiovascular risk, anxio-depressive disorders and overall diminished quality of life and sexual health in the future.

Pediatric and adolescent gynecological clinical encounters should incorporate prevention very early on, discussed in a personal way, encouraging high levels of self-esteem and positive sexuality.

Current research and future developments

I am currently running several research projects in the domains of contraception and adolescent sexual health. In terms of primary prevention, I am the principal investigator in two randomized controlled trials at the recruiting stage. The first study is assessing whether pretreatment with oral desogestrel before contraceptive implant insertion versus no pretreatment increases the continuation rate of implant users. The second study is comparing two different OCP formulations for the treatment of moderate to severe dysmenorrhea due to proven or suspected endometriosis in young adults, with bone mineral density as the primary endpoint assessment. In terms of secondary prevention, I led a systematic review on *Mycoplasma genitalium* in adolescents. In terms of tertiary prevention, I led a prospective study assessing the acceptance of using a fertility awareness tool in order to improve compliance to contraception in adolescents.

My goal for future research is to continue developing the evidence-base for prevention and sexual health among adolescents.

What is the Role of an Academic Clinical Educator in Pediatric and Adolescent Gynecology?

The PAG can disseminate knowledge for the promotion and implementation of prevention measures to adolescents in daily practice and to fellow gynaecologists, paediatricians and generalists.

For many adolescents who have not seen a paediatrician for years – particularly adolescent girls – the PAG is the first-line physician who is often the only link to healthcare. The roles and responsibilities of the PAG are therefore not only those of a sub-specialist, but also of a general health provider, assessing the adolescent in more holistic way and referring her when needed. For example, a consultation with a supposedly healthy girl should cover reproductive

health, but also other aspects of general health (obesity, headaches, hypertension anaemia, thromboembolic risk, etc.) and mental health (self-esteem, abuse, depression, eating disorders, etc.). These topics present opportunities to form links with other HCPs, particularly in university hospitals, and for teaching patient-centred care to students and residents in gynaecology, paediatrics, child psychiatry, and general medicine.

I have taken on numerous teaching roles and responsibilities in the last 14 years in Geneva University Hospitals and Faculty of Medicine. I have focused on incorporating prevention into medical education with the goal of building a strong foundation for positive sexuality and healthy future reproduction among adolescents. During the pre-graduate years, I have been a tutor and was recently elected as being co-responsible for the unit on reproduction for 2nd-year medical students. This has required the update and development of new learning materials that exemplify prevention in many aspects of clinical practice. I also present an *ex cathedra* lecture on contraception that illustrates how the burden of unplanned pregnancy can affect the development of an adolescent on a long-term basis. In addition, I have been teaching 4th-year medical students during their clinical years about contraception and sexual health.

Post-graduate teaching offers many opportunities for an academic medical educator specialized in PAG. I am very involved in teaching residents and fellows in both gynecological and pediatric programs on topics including pubertal and sexual development and its variations, disorders of sexual development, vulvo-vaginal disorders in the pediatric population, menstrual pathologies (irregularity, dysmenorrhea, heavy menstrual bleeding, and premenstrual syndrome) and PCOS in adolescents. In addition, I organize and lead workshops on LARCs, emergency contraception, how to communicate with adolescents, and caring for victims of sexual abuse. Regarding continued education, I have been a speaker/teacher at courses all over Switzerland on STIs in adolescents, contraception, and adolescent sexuality attended by family doctors and pediatricians from hospitals and private practice as well as, teachers and sexual educators from schools in the Geneva region.

My scientific contribution to the field is aligned with my overarching aim of developing evidence-based tools for prevention in PAG and supporting a positive approach to adolescent sexuality. Indeed, my recent publications focus on parent communication to children and adolescent about sexuality, and support for clinicians about STIs, IUDs and PCOS. My expertise in the field has been recognized and I was invited to write two chapters in textbooks: one on adolescent pregnancy in Switzerland published by Springer Publishing Company in 2014 in "*The International Handbook on Adolescent Pregnancy: Medical, Psychological and Public Health Responses*", and another about heavy menstrual bleeding, which was published in in 2018 by Cambridge University Press in a major reference book, "*Pediatric and Adolescent Gynecology - A Problem-Based Approach*". In terms of mentorship, I have supervised several master theses from medical students in my university on the same topics, with the goal of engendering interest and awareness for future generations of clinicians.

In addition to my academic teaching, my university activities include establishing connections with the Geneva community and transmitting knowledge to children and adolescent in schools and high schools. I am collaborating with the University of Geneva's, *Bioscope,* which aims to share scientific discoveries with the community through a series of public laboratories, which offer a new way to discover the world of scientific research through practical activities. In the latest project "Sexes, Sciences and Identity", I am a member of the committee and an invited speaker at several events on the topic of positive sexual education to adolescents. I have also participated in the development of information for the general public, and adolescents in particular, on positive sexuality, inclusiveness, and prevention.

While writing this thesis, I have realized how empowerment is an essential ingredient for prevention, particularly for adolescents and young adults. A sense of empowerment can be engendered and transmitted by doctors, parents, educators, and adolescents when using correct nomenclature, dispelling myths around HPV vaccination and IUDs, and informing and raising awareness of STI and PCOS, all while safeguarding confidentiality. Thus, prevention could support positive sexuality.

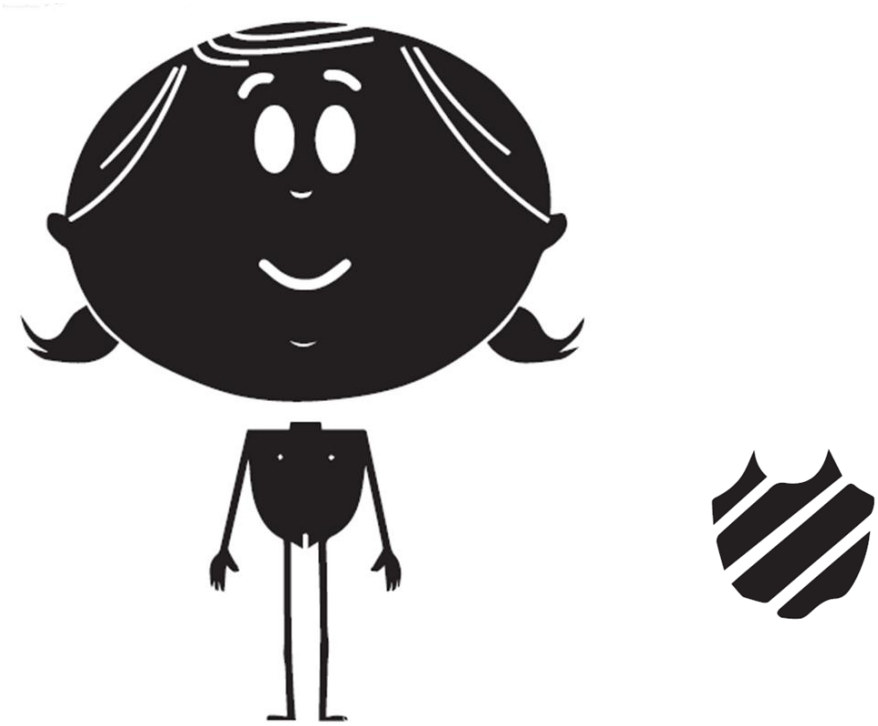
Vision for the future

In the coming years, I would like to continue to focus on supporting HCPs and educators to prioritize adolescent sexuality. Sexuality is a normal part of life for most human beings. Making sexuality an integral part of adolescent lives can be achieved routinely through an open dialogue about sexual matters in a developmentally-appropriate manner and with pre-established confidentiality. Discussions about sexual matters should go beyond prohibition and threat (STI and pregnancy), and instead promote intimate relationships and behaviours in a positive light (sexual attraction, pleasure, healthy relationships where respect and consent are the rule). In order to pursue this objective, HCPs need to act as a reliable source of information for these young adults and their parents. I have committed to teach in the paediatric and gynaecological post-graduate program for young residents, as well as pre-graduate medical students, and to run different workshops around gynaecological aspects of prevention that can be helpful for their post-graduate education. Consolidation of this priority may become evident with the creation of a dedicated unit for paediatric and adolescent gynaecology under the auspice of new the department of Woman, Child and Adolescent in the University Hospitals of Geneva.

I hope that, in the future, adolescents in Geneva and beyond will receive evidence-based information and competences on sexuality necessary for their well-being, essential for a full-lived life, in a world where sexuality is omnipresent.

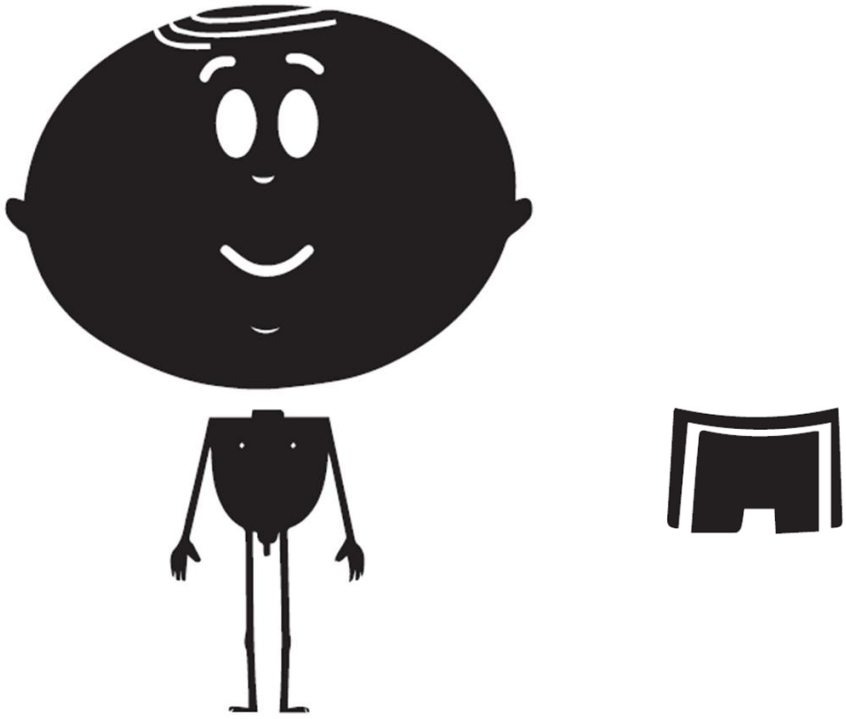
FIGURES & TABLES

Figure 1 Illustration of Anatomically Correct Sketches of a Girl and her "Private Parts" Covered by a Bathing Suit



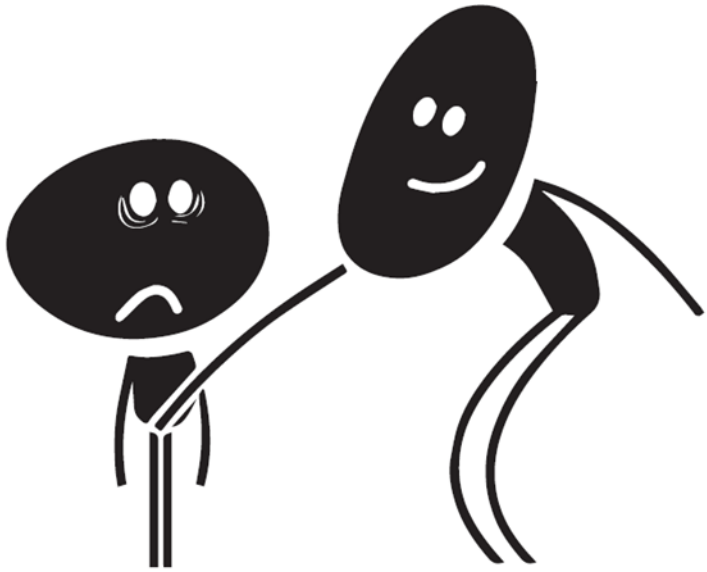
Reproduced from : Direction régionale de santé publique de la Capitale-Nationale et Direction régionale de santé publique de Chaudière-Appalaches, Les petits découvreurs de la sexualité! Activité pédagogique préscolaire en prévention de l'agression sexuelle, Guide de l'enseignant, Québec, 2014

Figure 2 Illustration of Anatomically Correct Sketches of a Boy and his "Private Parts" Covered by a Bathing Suit



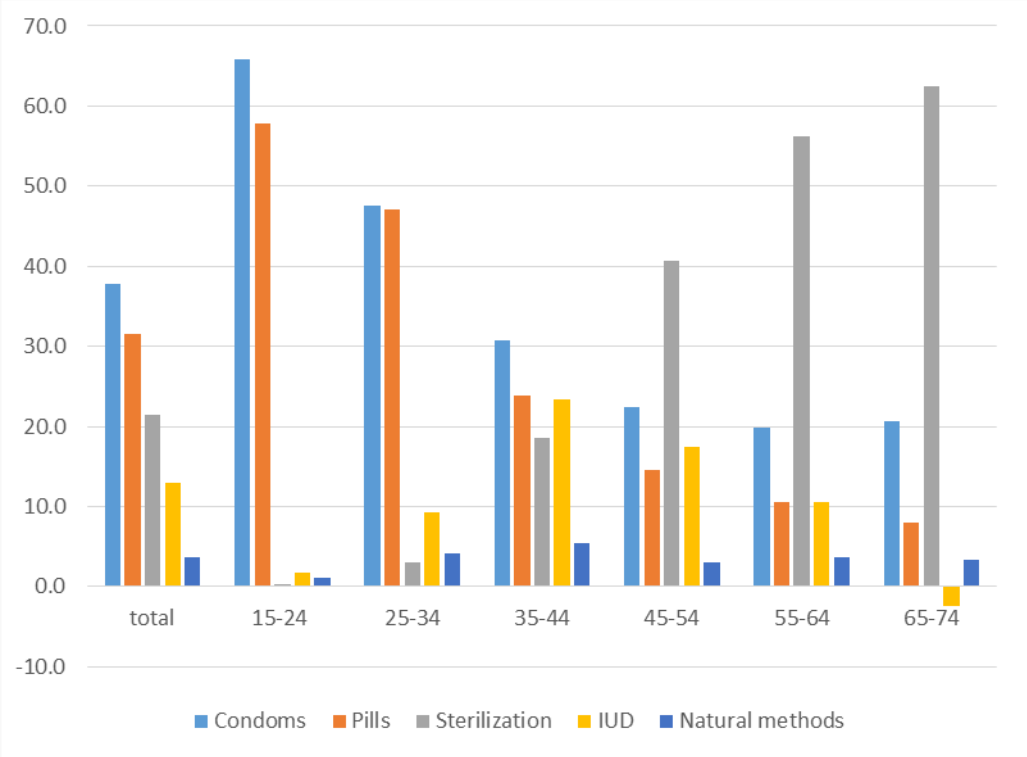
Reproduced from : Direction régionale de santé publique de la Capitale-Nationale et Direction régionale de santé publique de Chaudière-Appalaches, Les petits découvreurs de la sexualité! Activité pédagogique préscolaire en prévention de l'agression sexuelle, Guide de l'enseignant, Québec, 2014

Figure 3 Illustration of an Adult Touching Without Reason the Private Parts of a Child



Reproduced from : Direction régionale de santé publique de la Capitale-Nationale et Direction régionale de santé publique de Chaudière-Appalaches, Les petits découvreurs de la sexualité! Activité pédagogique préscolaire en prévention de l'agression sexuelle, Guide de l'enseignant, Québec, 2014

Figure 4 **Distribution of the Different Contraceptives used by Swiss People According to a Survey Conducted in 2012 by the Federal Office of Statistics**



Reproduced from Swiss health survey, 2012, OFS 2014

Table 1 Frequently Asked Questions and Answers about HPV Vaccination

What does HPV vaccination protect from ?	HPV is a common infection that has potentially serious consequences such as cervical, vaginal, vulvar, penile, anal, mouth, and throat cancer, and genital warts. The HPV vaccination protects against the most common HPV types (2 in Cervarix, 4 in Gardasil, 9 in Gardasil-9) HPV can induce a pre-cancer state which can progress to cancer. Thanks to HPV vaccination, pre-cancer states and cancer are prevented .
How is HPV transmitted ?	HPV can be transmitted by vaginal, oral or anal sex and by petting
What kind of vaccine is it?	HPV vaccine is an inactivated (not live) vaccine.
How safe is HPV vaccination ?	The HPV vaccination is extremly safe. Since 2006, more than 270 million vaccines were given world-wide. Since the vaccine was licensed, 0.0003% of patients have reported adverse effects—and most were not serious, such as headache, nausea and dizziness.
How effective is HPV vaccination?	Data shows that protection from pre-cancer stages and warts reaches 99% if the vaccine is administered before the first sex.
Are there studies proving HPV vaccination protects against cancer?	The progression from HPV infection to cancer development may take 10-20 years. To this day, no studies yet have been published, but first results are anticipated in 2019-2020. Experts expect >90% protective effect against cervical cancer, given a reduction of 90% against cervical dysplasia
How long does the HPV vaccination work?	Ongoing research shows that the HPV vaccine's protection remains for 8–10 years. There is no evidence to suggest this level of protection changes over time.
At what age should vaccination be carried out?	Vaccination is most efficient if given before the first sexual contact. Best if given between 11-14 years of age. Vaccination can begin as early as the age of 9 years. If vaccination begins before the 15th birthday, only 2 vaccinations are necessary . Among women aged 15 to 26 years, vaccines reduced the risk of pre-cancer cervical lesions associated with HPV16/18
Can HPV vaccination be introduced with other vaccinations at the same time ?	Yes

If I am already HPV-positive, do i still need to be vaccinated?	Persons who have already been infected with HPV may benefit from vaccination, because the probability that they are already infected with all 4 HPV types present in Gardasil 4v or the 9 HPV types 9v present in the different vaccinations is very small.
If I practice safe sex, do i need to be vaccinated?	Using condoms protects only partially against HPV infection, because the virus could be transmitted by direct skin to skin contact not covered by the condom.
Is Gardasil-9 better than the previous Gardasil?	Gardasil-9 covers 9 HPV types which are responsible for >90% of HPV-related cancers compared to only 4 HPV types.
Can the HPV vaccine be effective after one shot?	The HPV vaccine can reduce certain HPV-related cancers by up to 99% but only after administration of all doses.
If I vaccinate my child does it translated into earlier sexual activity ?	Studies on girls aged 11–12 years have found that HPV vaccination is not linked to increased sexual activity, and their antibody response was most robust if vaccination occurs during this time.
Can I have a 3rd HPV vaccination with Gardasil-9, or do I need to complete a new series of vaccination with Gardasil-9 ?	If the vaccination regime has not been completed before, it can be completed with the new Gardasil-9 vaccine according to US recommendations.
Why are two doses recommended for 9–14 year olds, while older adolescents need three doses?	Studies have shown that two doses of HPV vaccine given at least six months apart to adolescents at age 9–14 years worked as well or better than three doses given to older adolescents and young adults.

Modified and translated from Dietrich L, Notter J,..., Yaron M, et al. Vaccination anti-HPV: mise à jour 2019 pour la consultation. *Swiss Medical Forum* 2019;19(1314):220-226

Table 2 Initial Intrauterine Device Counselling

Placement	An in-office procedure that requires the use of stirrups and speculum. Adolescent patients are counselled to take 600-800 mg Ibuprofen before placement, because the procedure can be uncomfortable. The uterus is measured and then the IUD is placed through the cervix.
Placement risks	Discomfort, uterine perforation, infection, bleeding. There are very low failure rates associated with use of IUD.
Hormonal (LNG) IUD menstrual bleeding	Regular menstrual cycles are interrupted. The ideal outcome with LNG-containing IUDs ranges from light, painless menses to complete amenorrhea. It is not uncommon to have persistent irregular menstrual bleeding, especially in the first 3 months. With time, IUD users generally proceed to lighter menstrual bleeding. Other possible side effects include: acne, breast tenderness/pain and headache that will often settle with time.
Copper IUD menstrual bleeding	As previously stated, the bleeding outcomes form the copper IUD can often be heavier than previous to IUD use for use in the adolescent population.
Follow-up	It is advisable to feel the threads at least once a month as the risk of expulsion is between 5-7%. Missed periods or amenorrhea associated with abdominal pain should be evaluated to exclude an ectopic pregnancy.
Obtain medical help	Presence of symptoms of pelvic infection, pain, abnormal bleeding, late menstrual period (IUD), non-palpable threads or can feel the stem of the IUD.

Reproduced and modified from Allen, S, Barlow, E. Long-acting reversible contraception: an essential guide for paediatric primary care providers. *Pediatric Clinics*, 2017; 64(2), 359-369.
Faculty of Sexual & Reproductive Healthcare Clinical guidance. Clinical effectiveness unit. Intrauterine Contraception. April 2015

Table 3 Clinical Classification of Pelvic Inflammatory Disease and Likely Microbial Causes

Clinical Syndrome	Causes
Acute pelvic inflammatory disease (<30 days duration)	Cervical pathogens *(Neisseria gonorrhoeae, Chlamydia trachomatis, and Mycoplasma genitalium)*
	Bacterial vaginosis pathogens *(peptostreptococcus species, bacteroides species, atopobium species, keptorichia species, M. hominis, Ureaplasma urealyticum, and clostridia species)*
	Respiratory pathogens *(Haemophilus influenzae, Streptococcus pneumoniae, group A streptococci, and Staphylococcus aureus)*
	Enteric pathogens *(Escherichia coli, Bacteroides fragilis, group B streptococci, and campylocacter species)*
Subclinical pelvic inflammatory disease	*C. trachomatis* and *N. gonorrhoeae*
Chronic pelvic inflammatory disease (>30 days duration)	*Mycobacterium tuberculosis and actinomyces species*

Reproduced from: Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. *N Engl J Med.* 2015;372(21):2039-2048.

Table 4 Optimal Diagnostic Procedures for Chlamydial and Gonoccocal Infections

Vaginal/cervical smear	The two sample sites have almost the same sensitivity.
	Vaginal smear: rotate the swab 3 times, scraping the vaginal wall.
	Cervical smear: before the Papanicolaou test; after removal of cervical secretions using cotton, introduce swab at least 1 or 2 cm inside the cervical canal and rotate twice scraping the wall.
Meatus/urethral smear	In men, urethral smear and meatus smear are as sensitivity as the first stream of urine.
Sample of urine	First stream, maximum 20 ml.
	Sample at least one hour after the last urination.
	In women, less sensitivity than cervico-vaginal smear.
Anal smear	No lubricant or local anaesthetic.
	With a slight rotation movement, introduce the swab deep enough (3 to 5 cm; the wadded part should not be visible). With a careful rotation movement and a slight pressure during 30 seconds, scrape the anal wall to increase the absorption of chlamydia and gonococci by the cotton tip.
Pharyngeal smear	Scrape carefully the posterior wall of the pharynx, including the tonsils.
Before sending the smear	Scrub during 15 seconds the cotton on the wall of the tube to extract the pathogens into the liquid.

Adapted from:

Toutous Trellu, L, Oertle D, Itin P, *et al.* Gonorrhée: nouvelles recommandations en matière de diagnostic et de traitement. *Forum Med Suisse*. 2014(20):407-409.

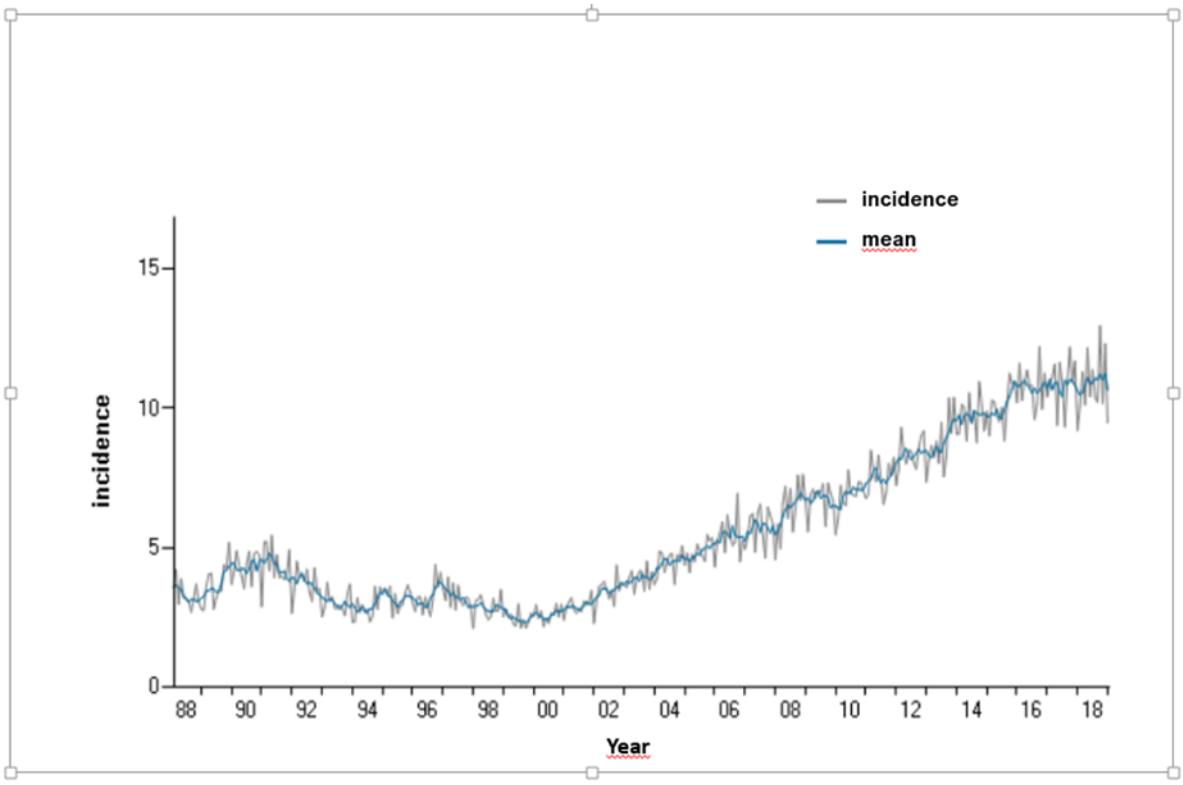
Notter J, Frey Tirri, B, Bally F, Aebi-Popp K, Yaron M…Tarr P, et al. Infections sexuellement transmissibles à Chlamydia trachomatis. *Swiss Medical Forum* 2017(17): 705-711.

Table 5 Recommendations for Treatment of Chlamydia Trachomatis Infections and Associated Pathogens Syndromes

Clinical	First-line treatment	Alternative	Comment
Genital chlamydia, uncomplicated pharyngeal or rectal infection	Doxycycline 100mg PO 2x/day during 7 days	Erythromycin 500mg 2x/day during 7 days	Partner treatment: treat current or previous sexual partners of last 6 months
	Azithromycin 1g PO, single dose	Levofloxacin 500mg 1x/day during 7 days	Avoid sexual intercourse during the first week following the start of treatment except if partner is simultaneously treated
		Ofloxacin 200mg 2x/day during 7 days	In case of rectal infection, doxycycline is preferred
			Therapeutic control by PCR not sooner than four weeks after the end of the treatment
Venereal lymphogranuloma	Doxycycline 100mg PO 2x/day during 3 weeks	Azithromycin 1g 1x/week during 3 weeks	In men having sex with men, HIV positive
		Erythromycin 500 mg 4x/day during 3 weeks	Ask for a specialist's view
Inflammatory illness	Ask for a gynecologist or infectiologist's view		

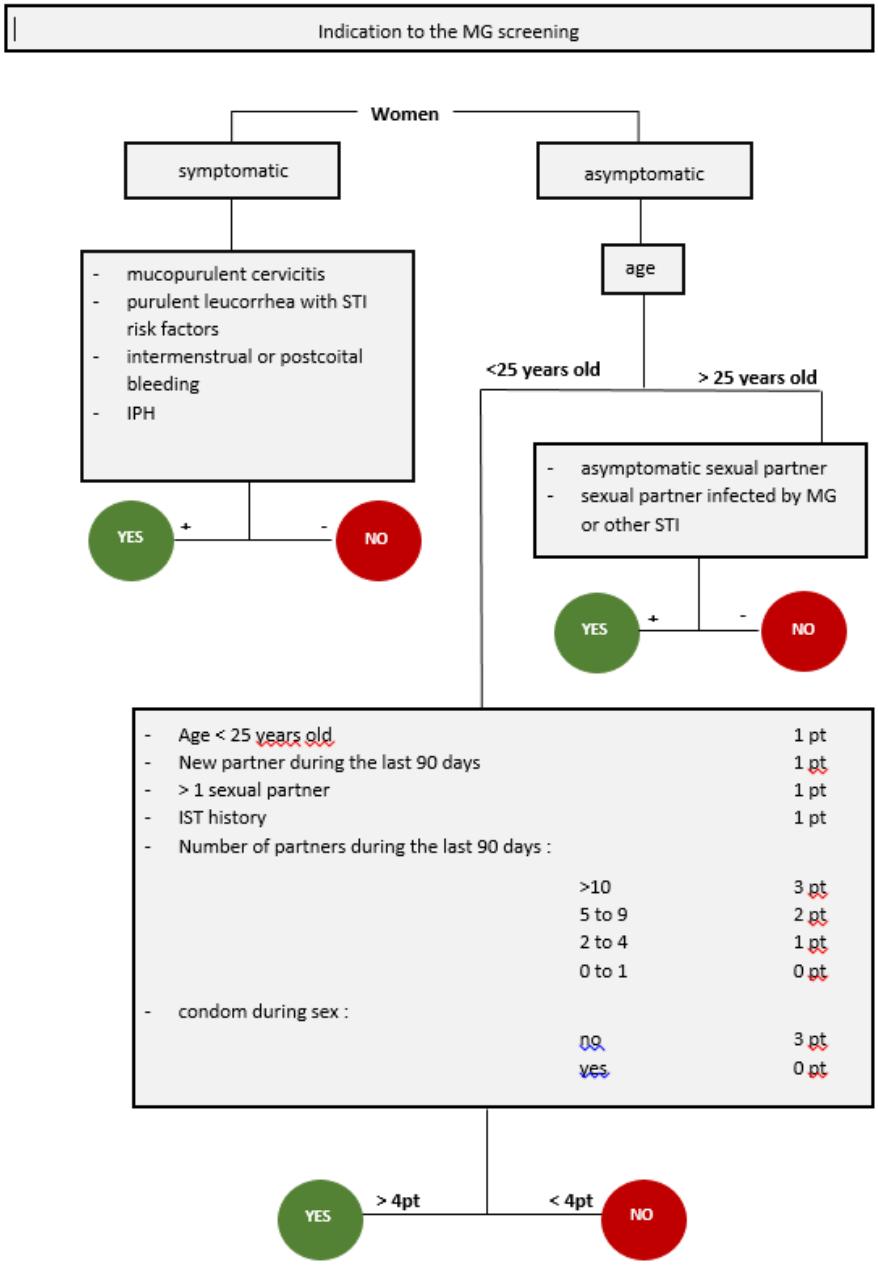
Reproduced and translated from: Notter J, Frey Tirri, B, Bally F, Aebi-Popp K, Yaron M…Tarr P, et al. Infections sexuellement transmissibles à Chlamydia trachomatis. *Swiss Medical Forum* 2017(17): 705-711.

Figure 5 **Annual Incidence of Chlamydia Trachomatis Infection per 100,000 Population from 1988-2018**



Reproduced and translated from : Office fédéral de la santé publique (OFSP) Division des maladies transmissibles, from 24.12.2018

Figure 6 Indication for Mycoplasma Genitalium Screening in Women



Translated and adapted from: Peter C, Alec M, Bigoni J, Toutous-Trellu L, Yaron M. [Update on Mycoplasma genitalium among women]. *Rev Med Suisse.* 2018;14(624):1893-1897.

Table 6 Suggested Criteria for the Diagnosis of Polycystic Ovary Syndrome in Adolescence

<table>
<tr><th>Required</th><th>Optional</th><th>Not recommended</th><th>Comments</th></tr>
<tr><td>Irregular menses/ oligomenorrhea</td><td>PCOM</td><td>Obesity</td><td>Must generally be 2 years post-menarche</td></tr>
<tr><td rowspan="4">Evidence of hyperandrogenism:

a. Biochemical
(Free or total Testosterone)

b. Clinical
(e.g. progressive hirsutism)</td><td>Severe cystic acne</td><td>Insulin resistance</td><td>Must rule out other disorders of hyperandrogenism (e.g., NC-CAH, Cushing syndrome)</td></tr>
<tr><td rowspan="3"></td><td>Hyperinsulinemia</td><td rowspan="3"></td></tr>
<tr><td>Biomarkers (e.g., AMG, T/DHT ratio)</td></tr>
<tr><td>Acanthosis nigricans</td></tr>
<tr><td colspan="4">PCOM, polycystic ovarian morphology; AMH, anti-Müllerian hormone; T/DHT, testosterone to dihydrotestosterone; NC-CAH, non-classical congenital adrenal hyperplasia. These criteria are often used in concert with the required criteria, but should not be used independently as diagnostic features. These criteria have been associated with PCOS but are not diagnostic.</td></tr>
</table>

Reproduced from: Ibanez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. *Horm Res Paediatr.* 2017;88(6):371-95.

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