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Including adolescents of childbearing potential in clinical trials with possible exposure to teratogenic medication: a challenge for paediatricians and researchers

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Summary

The issue of contraception and pregnancy tests among minor adolescent women participating in clinical trials, whether healthy or suffering from a disease, represents a challenging issue for paediatricians and researchers, given the potential harmful effect of various therapeutic procedures being tested. First, they need to gauge at what age or developmental stage they need to impose pregnancy tests and contraception. Second, if the adolescent denies any sexual activity, it may be ethically questionable to impose such procedures. Third, these professionals must deal with the issue of confidentiality, taking into account the fact that some adolescents engage in penetrative sexual intercourse without their parents or caregivers knowing. Fourth, in such cases, they must assess the extent to which a minor adolescent can be considered as competent (capable of making autonomous decisions) and deserves privacy and confidentiality. There is indeed a legal obligation for the provider to check that sexual experiences and intercourse take place within a safe relationship. Fifth, if the prescription of contraception is warranted, they have to decide who should assist the adolescent in choosing the method. Finally, with the occurrence of a positive pregnancy test, they may face the rare instance of a competent minor adolescent who refuses to inform her parents. This article has been developed by a group of experts under the auspices of swissethics, the Swiss Association of Research Ethics Committees and SwissPedNet, the umbrella organisation that coordinates the paediatric research in Switzerland. The paper reviews how to address practical and ethical questions regarding minor adolescents of childbearing potential enrolled in a clinical trial that may involve teratogenic medication and offers a series of concrete advice and tools for dealing with problematic situations.

Most paediatric protocols stipulate that adolescents included in clinical trials involving potentially teratogenic drugs should undergo pregnancy tests and use contraception. The circumstances in which such requirements are undertaken, however, has not been sufficiently addressed.

The recommendations presented in this article will assist researchers in assessing which circumstances apply when considering minor adolescents as individuals with childbearing potentials. It also offers concrete suggestions for tackling such situations.

Keywords: *adolescent*, *ethics*, *competence*, *female*, *childbearing*, *menarche*, *pregnancy*, *contraception*, *clinical trial*

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Introduction

The issue of contraception and pregnancy among women participating in clinical trials, whether healthy females or individuals suffering from a disease, is an important topic, given the potential harmful effect of the various therapeutic procedures tested. As stated by the European Medicines Agency "precautions to prevent pregnancy include pregnancy testing (e.g., based on the β-subunit of human chorionic gonadotrophin), use of highly effective methods of birth control and study entry only after a confirmed menstrual period, and in most instances, protocols require the use of an effective contraception during the trial and for some time after completion of the trial, among females, in several occurrences among males or partners as well" [1]. This theoretically applies to minor adolescents of childbearing age, but in reality such principles are not easy to respect as there is not any age limit for the acquisition of fertility nor for an adolescent to be granted competence [2–4]. Indeed, defining an adolescent at 14 years of age in the Federal Act on Research involving Human Beings is arbitrary and is not helpful in determining whether an ado-

lescent girl must be considered of childbearing age. The brochure recently issued by swissethics on clinical trials among healthy children and adolescents does not provide guidance in this respect [5], and the recent international guidelines and recommendations fail to offer sound strategies regarding how to address the issue of sexual life of minors of childbearing potential [3, 5–11]. Moreover, protocols are not always explicit as how to deal with this matter.

The objective of this article is to provide guidance for what to do in cases involving minor adolescents of childbearing age enrolled in clinical trials including the use of potentially teratogenic drugs or devices. Its content is applicable to the prescription of medication or procedures that are licensed by Swissmedic but have a teratogenic potential. Although male adolescents do not bear children, part of the assessment procedure described in the last part of this article may apply to them as well given that many trial protocols also request contraception from fertile male participants.

Adolescent puberty and reproductive health

Since Tanner's seminal work describing the stage of pubertal development, paediatricians and other health practitioners identify the progress of puberty using a simple clinical/physical assessment of the growth of genitals and secondary sex characteristics [12]. Any female adolescent who has a pubertal development at Tanner stages 3 to 5 is potentially able to become pregnant. This is even the case for females who are not menstruating, although this is not common [4, 13]. Theoretically, assessing Tanner stage (fig. 1) is not difficult but it is a sensitive issue, as the direct examination of hairiness, of the breast and of the external genitals can be experienced as an intrusive procedure [14]; thus it is important for the healthcare provider to explain why this information is needed and also to present the adolescent with the option to have the examination made with or without the presence of the parents or a chaperone. An alternative is to use drawings of the five stages (fig. 1) or ask the adolescent to self-assess his stage [15]. Indeed, while pregnancy can theoretically occur by Tanner stage 3 (e.g., around the age of 10–12 years for most girls), the majority of adolescents do not engage in intimate sexual activities, including active/penetrative sexual intercourse before the age of 15 or later. According to the most recent available data, in Switzerland, the mean age for first sexual intercourse is 16.4 years among boys and 16.7 among girls [16].

As many trials last for several years, professionals including very young adolescents in their research should not forget that an adolescent could engage in sexual intercourse any time over the duration of the trial. This is all the more important to keep in mind as the young persons' behaviours are often unexpected and unpredictable [17, 18], In addition, while many professionals think that adolescents with a chronic condition do not engage in exploratory behaviour (such as using drugs or having sex), this is wrong: young people with chronic conditions do adopt such behaviours as much or even earlier than their healthy peers [19, 20]. In other words, an abstinent adolescent at the inclusion in a clinical trial may become sexually active over time, a situation that needs to be regularly monitored.

Clinical trials with minor children of childbearing potential

Most protocols for investigational drugs stipulate that women of childbearing potential must use a recognised method of contraception. They usually request pregnancy tests and the use of a combination of chemical and barrier methods; moreover, in most cases abstinence is not acceptable. This theoretically applies for childbearing potential adolescents as well. However, the situation of minor adolescents requires a specific approach: on one hand, their parents must be able to exercise their educational rights and duty. On the other hand, in Switzerland, minor adolescents, as long as they can be considered as competent ("capable of judgement" according to article 16 of the Swiss Civil Code) have the right to privacy and confidentiality and to consent to healthcare procedures. Minor adolescents commonly do not disclose sexual experiences to the parents or caregivers, at least initially, so it is important for this information to be gathered in a secured, empathetic and confidential atmosphere [21]. Such confidential care is granted to any adolescent who is considered competent, meaning able to reflect appropriately and make autonomous decisions [3, 7, 22, 23], in accordance with the United Nation Convention on the Right of the Child (CRC) [24]. At the same time, however, raising the issue of a contraception and pregnancy test requirements comes as a shock to some parents or guardians and may deter them from giving permission to participate in the trial. In addition, all professionals engaged in clinical trials involving childbearing potential should be aware of the fact that the meaning of sexuality and of adolescent sexual behaviour differs widely from one culture or religion to another [25, 26]. Thus, these issues must be discussed in a respectful atmosphere and the investigator should carefully explore both the adolescents' and the parents' views.

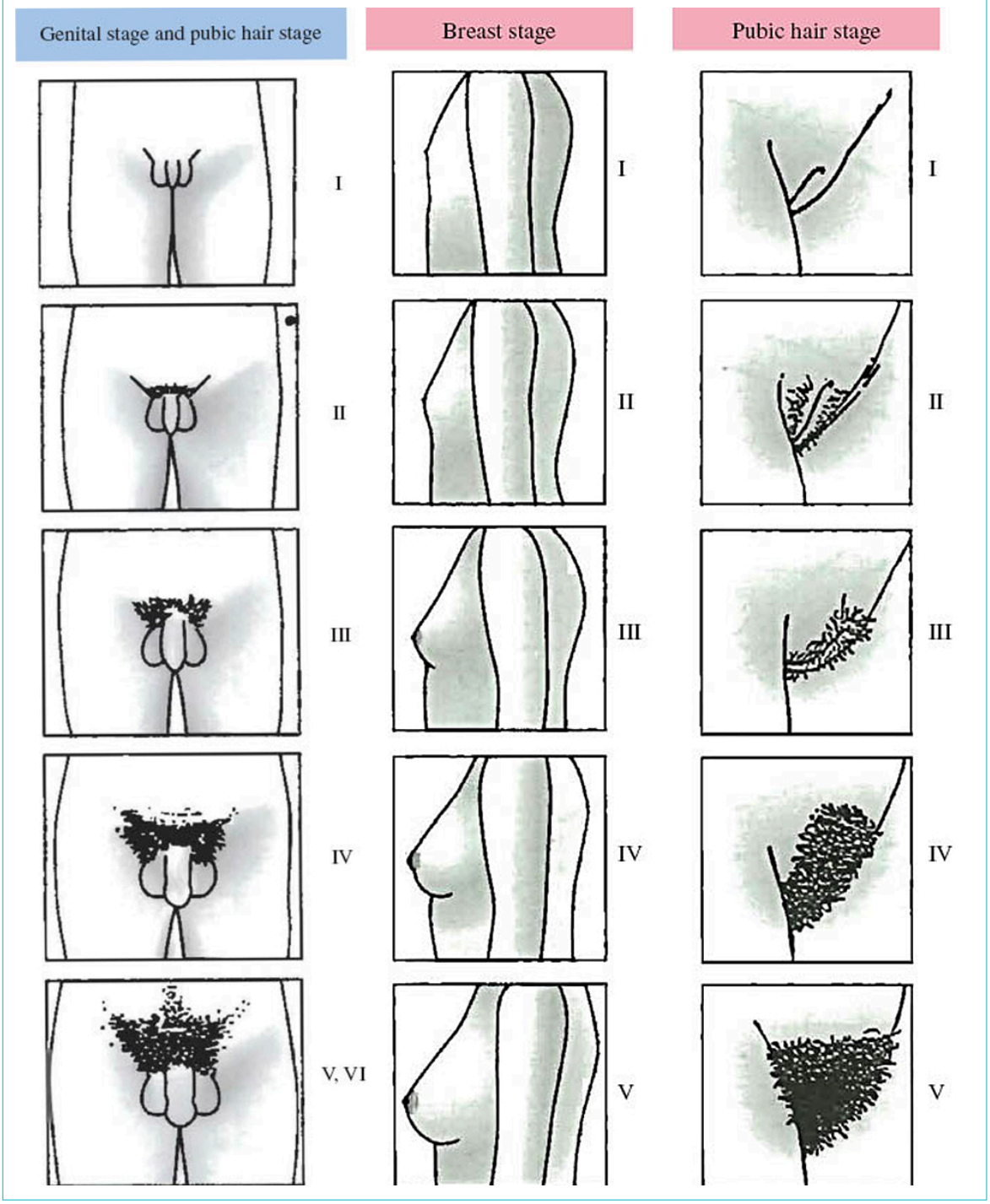
How to evaluate the situation

The evaluation of minor adolescents of childbearing potential involves several legal, psychological and ethical questions that need to be explored; in some instances, this may be better processed by an inter-professional team involving the primary care practitioner, the Principal Investigator or his collaborators, or a psychologist and a gynaecologist with an experience in child and adolescent bio-psychosocial development [2, 27]. Special attention should be paid to the involvement of the parents and caregivers, and, above all, to the rights and opinions of the young person herself [24, 28]. This careful and respectful approach of adolescent healthcare has been reaffirmed in several recent Comments made by the Office of the High Commissioner of the UN Human Rights: the General Comments 12 (2009) on the rights of the child to be heard, 14 (2013) on the right of the child to have his or her best interests taken as a primary consideration, and to some extent 20 (2016) on the implementation of the rights of the child during adolescence. Additionally, the Council of Europe has recently published guidelines on child-friendly healthcare that stress the importance of respecting the child's dignity and protecting his or her involvement in decision making, as well as delivering healthcare in the best interest of the child [29].

Assessing the adolescent's competence, rights to consent or assent, behavior and situation

It is not easy for practitioners caring for a sexually active minor adolescent to decide whether she should enjoy the benefits of autonomous decision-making capacity (i.e., "competence" in legal terms). The HRA (Human Research Act) sets the limit between childhood and adolescence at 14 years of age. However, given the broad range of cognitive and affective development among children, this does not mean that individuals younger than 14 years are not competent, nor are all individuals older necessarily competent in all situations [27]. Moreover, competence varies depending on the complexity of the situation: it is indeed different to provide confidentiality for an interview on lifestyles or for the decision to undergo an abortion or to continue a pregnancy. The assessment of an adolescent's competence is a process that should be carefully conducted, often over more than one encounter [3, 30–33]. It can be performed first in delivering information on issues such as knowledge of the disease, effect of the treatment, purpose of the trial, etc. Then, the health professional may take time to ask questions of the adolescent and thus evaluate his understanding of the situation (e.g., asking the patient to reformulate the information), his capacity to reason

Figure 1: A schematic drawing of the five Tanner stages for girls and boys. From: Jaruratanasirikul S, Kreetapirom P, Tassanakijpanich N, Sriplung H. Reliability of pubertal maturation self-assessment in a school-based survey. J Pediatr Endocrinol Metab. 2015;28(3-4):367-74, reprinted with permission.



on the pros and cons of various options, and his ability to make choices and justify why and how the choices are made. This process allows, at least to some extent, the healthcare provider to appraise the adolescent's cognitive and emotional functioning [3]. Research collaborators who are not experienced in performing such an assessment should ask for the support of senior experienced colleagues with some training in adolescent medicine. Any adolescent assessed or considered as competent is entitled to benefit from privacy and confidentiality and is also free to give consent to any health decision or procedure.

Informed consent means approval of the legal representative of the child and/or approval by a competent child for medical interventions and procedures following appropriate information. According to Art. 23 HRA, the adolescent above 14 years can consent alone only if the research is associated with minimal risks. Informed assent means a child's agreement to medical procedures in circumstances where he or she is not legally authorised or lacks sufficient understanding for giving formal consent [34, 35]. Even young children deserve explanations around medical procedures and must be invited to give an opinion or an assent, as mentioned by the CRC [24] and Art. 6 of the 1997 Council of Europe Convention on Human Rights and Biomedicine. Medical procedures should not be imposed to children unless there are important health reasons to proceed; and delivering information in warm and respectful climate is helpful for obtaining an assent from the child (e.g. vaccination, venipuncture etc.).

Exploring the adolescent's health behaviour and lifestyle

The investigation of the adolescent's health behaviour, psychosocial background and situation should be empathetic, non-judgmental and progressive. It is possible to obtain credible answers for any health area, including sexual behaviour, as long as confidentiality is maintained [21, 31, 36]; however, the reasons for these questions should be carefully explained. As mentioned in table 1, the discussion should start with inquiries around family life, sport and leisure, social activities, expectations regarding the future and then move on to more intimate issues such as puberty, menstruations, and opinions regarding sexuality [37]. This allows for a smooth transition and establishes a climate of confidence and understanding that allows the professional to move on and ask straightforward questions such as: "Some girls of your age have sexual experience or intercourse, do you know of such situations?"; "What about you?"; "Have you ever had a sexual experience?"; "How do you feel about having sex?"; "Have you ever had sexual intercourse?; "When do you imagine that it will happen?";"What would you do if you are asked to or have had sexual intercourse?" and so on. The questions should not be asked as a kind of checklist, but rather be brought up according to the adolescent's stage of development, cognitive capacity and reactions during the interview. It is often very useful to ask the adolescent how she feels about some of her behaviour or experiences to appraise her cognitive skills and maturational stage.

Delivering the information pertaining to the trial to the adolescent and to the parents

Besides the written documents that are provided to the parents and the adolescents, the Principal Investigator or one of his delegates usually delivers an oral overview of the information and responds to questions about the trial. This is all the more important if the adolescent is of childbearing potential. Oral information targeting the adolescent should be adapted to her age and developmental stage. It is not acceptable to provide such information in a kind of "top-down" attitude; rather, the healthcare professional should ask the adolescent to reformulate with her own words what has been understood [3, 5, 14, 28, 31, 37–39]. The adolescent should be encouraged to disclose her understanding of the situation, ask questions about her illness, the treatment or trial and the prognosis [15, 16, 21, 27, 40–44]. If an adolescent discloses active/penetrative sexual intercourse without the parents knowing, confidentiality could be maintained as long as the adolescent can be considered competent, but in all circumstances, the adolescent should be strongly encouraged to disclose her situation to her par-

Table 1: Some examples of how to assess an adolescent's health habits and lifestyles, using the HEEADSSS acronym [37].

Home: Who do you live with? Do you have your own room? What are relationships like at home? Who are you closest to at home?
Education and employment: What do you like most about school? Tell me about your friends at school. What are your favourite subjects at school? How are your grades? What are your future education, employment plans/ goals?
Eating: What do you like and not like about your body? Have there been any recent changes in your weight? Have you dieted in the last few months? How? How often? What do you think would be a healthy diet? How does that compare to your current eating patterns? Do you worry about your weight? How often?
Activities: What are your favourite activities? What do you and your friends do for fun? (who with, where, and when?); What do you and your family do for fun? (who with, where, and when)? Do you have a "best" trusted friend? How do you get along with your mates? How much exercise do you get on average per day or per week? How much time do you spend on screen/ the internet, and what for?
Drugs: Do any of your friends use tobacco, alcohol or other drugs? What about you? If you do smoke, how do you feel about it? Have you ever thought about quitting? If you drink alcohol, would you allow us to discuss it? How often do you drink and under what circumstances? Have you ever been drunk? Similar questions can be used for cannabis or other illegal drugs.
Sexuality: Have you ever been in a romantic relationship? If you are comfortable with it, tell me about your sex life. Have any of your relationships ever been sexual? What about you? What does the term "safer sex" mean to you? Are you interested in boys? Girls? Both? Have you ever been forced or pressured into doing something sexual that you did not want to do?
Suicide and depression: Are you often anxious? What makes you anxious? Do you feel sad or down more than usual? Do you find yourself crying more than usual? Are you "bored" or tired all the time? Does it seem that you have lost interest in things that you used to really enjoy? Do you find yourself spending less and less time with friends? Are you having trouble getting to sleep? Have you thought a lot about hurting yourself or someone else? Have you ever thought of committing suicide? Alternatively, have you ever attempted?
Safety: Have you ever been seriously injured? How? How about anyone else you know? Do you always wear a seatbelt in the car/ use a helmet while biking or using a motorbike or while snowboarding? Have you ever ridden with a driver who was drunk or high? Is there violence around you? Have you ever been physically or sexually abused?
Social media: Do you have your own computer, tablet, or mobile phone? How do you use them? Are there any rules set by your parents/caregivers regarding use of ICTs (information communication technology); does your use of ICT generate conflicts at home? Do you have your own rules regarding such use? Is there an issue regarding your use of ICT that disturbs you?

ents or caregivers, especially if she is under 14 years of age.

The information delivered to the parents should be as comprehensive as possible. Besides the usual material regarding the design of the trial, the medication or the device, the parents should be notified that the protocol requires a thorough review of the adolescent's lifestyle, including the adolescent's understanding of the disease, adherence to treatment, as well as broader health issues, such as lifestyles and sexual behaviour. If relevant, parents should be notified if the trial will require providing contraception and performing pregnancy tests. They should understand why it is important to have a discussion with the adolescent alone, keeping in mind that the adolescent will be encouraged to disclose most or all of the content of the confidential exchange. This procedure could be presented as a "routine", to avoid angry reactions from the parents; it should also be undertaken with an awareness of the cultural and religious background of the family [26]. This applies to any adolescent, irrespective of her Tanner stage and age, as adolescents have the right to be considered and treated as "subjects" with her own ideas, representations and wishes [24].

Making decisions regarding the involvement of adolescents with childbearing potential: a concrete approach

The professional(s) who will perform the assessment of the situation should be identified prior the beginning of the study and have experience in adolescent medicine and health. Figure 2 provides an algorithm that should assist the investigators in making decisions. As many trial protocols also request contraception from fertile male participants, part of the assessment procedure described below may apply to them as well (first bullet points).

- First, one needs to assess the Tanner stage of the adolescent. This is part of the usual assessment of the adolescent's situation that has to be maintained over the whole duration of the trial or treatment. Figure 1 provides a description of the five Tanner stages. Adolescents whose pubertal development is above stage 2 should be considered as childbearing potential individuals, irrespective of the occurrence of menarche.
- Next, the health professional needs to investigate in a confidential setting (at least when dealing with intimate matters) the lifestyle of the adolescent as described in table 1. This procedure can be applied to adolescents Tanner stage 1 and 2, as it helps the researcher to anticipate future issues in regards to lifestyle and sexual behaviour; the content of the review must, of course, be adapted to the adolescent's cognitive and affective stage.
- For adolescents Tanner stage 1 or 2, or those above not disclosing *any* current or foreseen heterosexual activity, it is acceptable to rely on abstinence, as long as it is made clear that the issue of sexual behaviour will be monitored on a regular basis (often including repeated "routine" pregnancy tests, as frequently required by the protocol).
- If the adolescent is over Tanner stage 2 and if the information that he delivers does not seem reliable, or if the adolescent is considering sexual activity in the near or middle-term future, or if she discloses a sexual activity (e.g., intimate exchanges, sexual intercourse), a pregnancy test should be performed. This is presented as a routine, to avoid concerns or "outraged" reactions from the parents or the adolescent.
- If the test is negative, the adolescent should be referred to a gynaecologist, a specialist already known, or, even better, a specialised adolescent gynaecologist, to investigate the situation and decide if, and what contraception can be offered and promoted [43, 45]. As adherence to oral contraception may be suboptimal during adolescence [46, 47], alternatives to the use of oral contraception or condoms should be proposed upfront, such as long-acting contraception [46–49] offering greater security (e.g., injectable, IUDs, implants) [45, 48, 49]. As is the case for older women, periodic abstinence (e.g., using calendar, ovulation, symptom/ thermal, post ovulation methods) and withdrawal are not acceptable [50]. If oral contraception is kept as an alternative, one should remember that, even if it does not affect fertility, contra-indications should be clarified by the gynaecologist. Moreover, the decisions must be taken in collaboration with the research team, as some medication (including those prescribed as part of a clinical trial) interfere with oral contraception.
- In some instances, the adolescent may not agree to disclose to the parents that she is sexually active. This is in principle acceptable for competent adolescents especially those who are 14 years of age or older. If the adolescent remains opposed to such a disclosure, and depending on her age, it may be an option to tell the parents that contraception is required by the protocol (with regular pregnancy tests); another option is to remove the adolescent from the trial. There is still a legal obligation for the provider to check that sexual experiences and intercourses take place within a safe relationship, at minimum to enquire about the age of the partner and the absence of pressure or violence. In addition, the investigator should keep in mind the fact that, in a very limited number of situations, disclosing the sexual activity of an adolescent to parents belonging to a community with moral values strongly banning sexual activities before marriage may lead them to send the adolescent back to the country of origin, enforce a marriage, or entail severe physical punishment and/or psychological abuse.
- Apart from the rare special circumstances just described above, sexually active adolescents, especially those under the age of 14, should be strongly encouraged to disclose to their parents the fact that they are sexually active: it often takes some time to convince the adolescent to do so. This requires specific skills and should be performed either by the gynaecologist or a trained researcher or collaborator of the healthcare team [51].
- If the pregnancy test turns out to be positive, the parents should, with very few exceptions, be informed of the situation, and the discussion will be the same as it would be for any adolescent facing an unexpected pregnancy [48–53]. Again, research collaborators who are not used to dealing with such situation should ask for the support of senior experienced colleagues with some

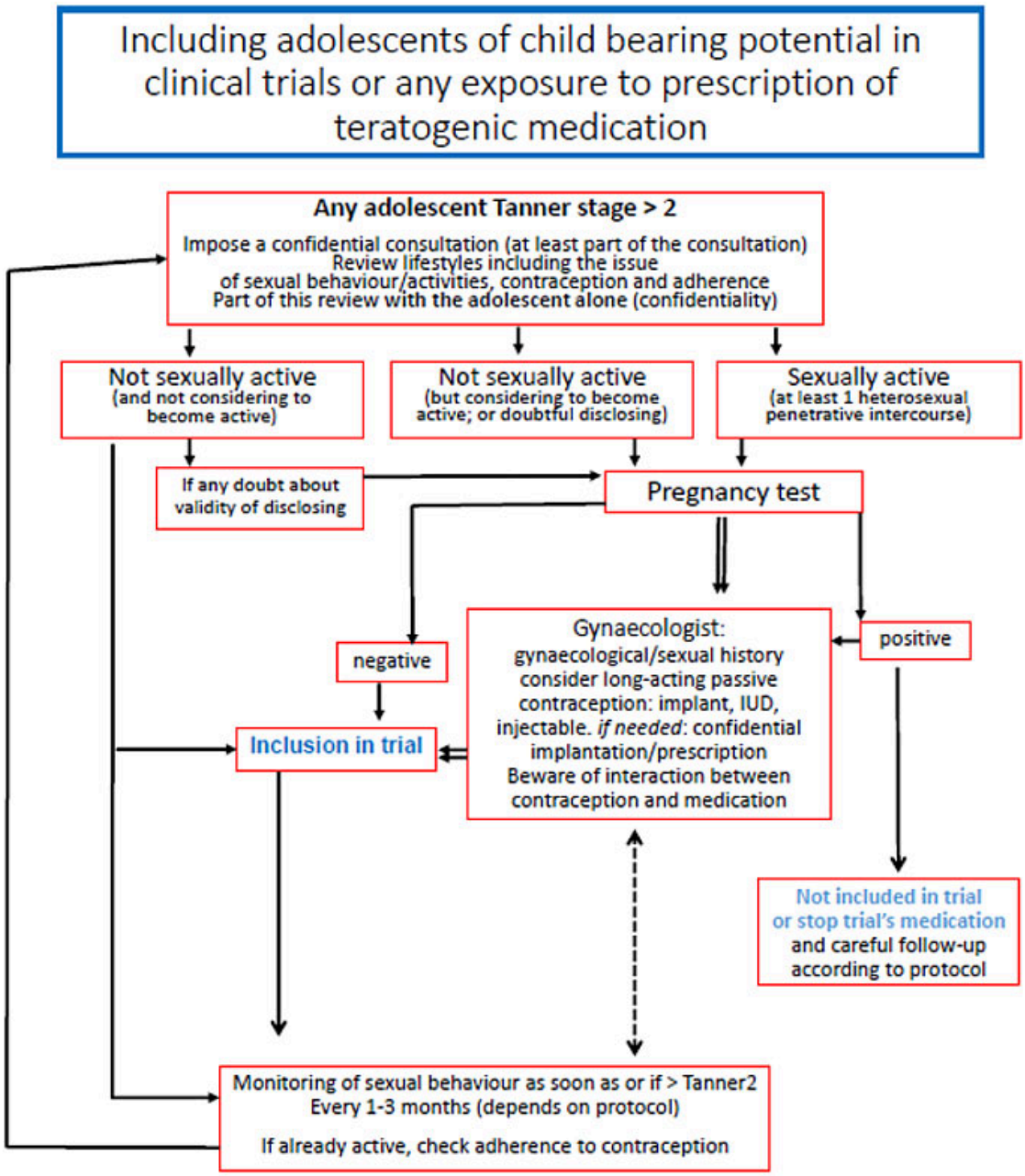
training in adolescent medicine. The adolescent should not be involved in the trial or be withdrawn from an ongoing trial and be referred to a gynaecologist and a social worker to discuss the issue of keeping the pregnancy or undergoing abortion. Nearly all such situations should be discussed with the parents/caregivers, and, if possible, with the male partner. In rare instances, with an adolescent displaying full competence, and if disclosing the pregnancy to the parents bears extensive potential risks for the physical or psychosocial health of the young woman, abortion can be performed with the support of a social worker or another trusted adult without the parents knowing. In Switzerland, most unexpected pregnancies are ended with an abortion [52]. Enrolment of the adolescent in the trial after having had an abortion is open to discussion, but should be considered only with an effective contraception, preferably of long-acting reversible type (IUDs, injectable, implants).

– If the pregnancy is continued, teratogenic therapies must of course be immediately terminated, or the adolescent should not be included in the trial.

Discussion

This article outlines the complex psychological and ethical issues presented by the involvement of adolescents of childbearing potential in clinical trials. It raises, among others, two major concerns. The first is the level of expertise required from the professionals who recruit adolescents in trials entailing teratogenic risk. Given the meagre time devoted to adolescent medicine and health in the training of paediatricians in Europe and Switzerland

Figure 2: A decision-making algorithm regarding the involvement of childbearing potential adolescents in clinical trials.



[54], some members of research teams may find it difficult to perform the tasks described in this article adequately. There are a growing number of sessions organised in Switzerland addressing adolescent healthcare, which could assist them in improving their skills. The second concern is linked with the fact that paediatric trial protocols, whether national or international, routinely mention the issue of contraception and pregnancy tests without providing any suggestions for how to concretely address the situation, such as which adolescents are concerned, who should perform the evaluation of the situation and how, and which professionals are involved. The process outlined in this article has been developed within the legal framework of Switzerland, which does not provide a fixed age limit for competence; this complicates the task of healthcare providers, but, on the other hand, respects the right of adolescents, as it grants minor individuals the possibility of making autonomous decision regarding their health, irrespective of their age [24]. Given the paucity of international recommendations in this regard, the authors hope to attract the attention of the international readership and stimulate more in-depth strategic reflection.

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References

1 European Medicines Agency. ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. London: European Medicines Agency; 2009. 26 pp.

2 Michaud PA, Berg-Kelly K, Macfarlane A, Benaroyo L. Ethics and adolescent care: an international perspective. Curr Opin Pediatr. 2010;22(4):418–22. doi: http://dx.doi.org/10.1097/MOP.0b013e32833b53ec. PubMed.

3 Michaud PA, Blum RW, Benaroyo L, Zermatten J, Baltag V. Assessing an Adolescent's Capacity for Autonomous Decision-Making in Clinical Care. J Adolesc Health. 2015;57(4):361–6. doi: http://dx.doi.org/10.1016/j.jadohealth.2015.06.012. PubMed.

4 Zhang K, Pollack S, Ghods A, Dicken C, Isaac B, Adel G, et al. Onset of ovulation after menarche in girls: a longitudinal study. J Clin Endocrinol Metab. 2008;93(4):1186–94. doi: http://dx.doi.org/10.1210/jc.2007-1846. PubMed.

5 Kleist P, Driessen S, Gervasoni P. Leitlinie zur Forschung mit gesunden Kindern und Jugenlichen. Bern: Swissethics; 2017.49 pp.

6 Modi N, Vohra J, Preston J, Elliott C, Van't Hoff W, Coad J, et al.; Working Party of the Royal College of Paediatrics and Child Health. Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees. Arch Dis Child. 2014;99(10):887–91. doi: http://dx.doi.org/10.1136/archdischild-2014-306444. PubMed.

7 World Health Organization. Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents. Geneva: World Health Organization; 2018. 52 pp.

8 World Health Organization. WHO recommendations on adolescent sexual and reproductive health and rights. Geneva: World Health Organization; 2018. 77 pp.

9 Graham A, Powell M, Taylor N, et al. Ethical Research Involving Children. Florence: UNICEF Office of Research – Innocenti; 2013. 220 pp.

10 Singh JA, Siddiqi M, Parameshwar P, Chandra-Mouli V. World Health Organization Guidance on Ethical Considerations in Planning and Reviewing Research Studies on Sexual and Reproductive Health in Adolescents. J Adolesc Health. 2019;64(4):427–9. doi: http://dx.doi.org/10.1016/j.jadohealth.2019.01.008. PubMed.

11 Santelli J, Haerizadeh S, McGovernz T. Inclusion with Protection: Obtaining informed consent when conducting research with adolescents. New-York: Mailman School of Public Health, Columbia University; 2017.18 pp.

12 Tanner J. Growth at Adolescence. 2nd. ed. Oxford: Blackwell Scientific Publications; 1962.

13 Gossain VV, Carella MJ, Rovner DR. Pregnancy in a patient with premature ovarian failure. J Med. 1993;24(6):393–402. [published Online First: 1993/01/01]. PubMed.

14 Coleman L, Coleman J. The measurement of puberty: a review. J Adolesc. 2002;25(5):535–50. doi: http://dx.doi.org/10.1006/jado.2002.0494. PubMed.

15 Berg-Kelly K, Erdes L. Self-assessment of sexual maturity by mid-adolescents based on a global question. Acta Paediatr. 1997;86(1):10–7. doi: http://dx.doi.org/10.1111/j.1651-2227.1997.tb08822.x. PubMed.

16 Barrense-Dias Y, Akre C, Berchtold A, et al. Sexual health and behavior of young people in Switzerland. In: Institut universitaire de médecine sociale et préventive, ed. Raisons de santé. Lausanne: IUMSP Institut universitaire de médecine sociale et préventive, 2018:116 pp.

17 Steinberg L. Age of Opportunity: Lessons from the New Science of Adolescence. New York: Houghton MifflinHarcourt Publishing Company; 2014.

18 Steinberg L, Morris AS. Adolescent development. Annu Rev Psychol. 2001;52(1):83–110. doi: http://dx.doi.org/10.1146/annurev.psych.52.1.83. PubMed.

19 Michaud PA, Suris JC, Viner R. The adolescent with a chronic condition. Part II: healthcare provision. Arch Dis Child. 2004;89(10):943–9. doi: http://dx.doi.org/10.1136/adc.2003.045377. PubMed.

20 Surís JC, Michaud PA, Akre C, Sawyer SM. Health risk behaviors in adolescents with chronic conditions. Pediatrics. 2008;122(5):e1113–8. doi: http://dx.doi.org/10.1542/peds.2008-1479. PubMed.

21 Pampati S, Liddon N, Dittus PJ, Adkins SH, Steiner RJ. Confidentiality Matters but How Do We Improve Implementation in Adolescent Sexual and Reproductive Health Care? J Adolesc Health. 2019;65(3):315–22. doi: http://dx.doi.org/10.1016/j.jadohealth.2019.03.021. PubMed.

22 Larcher V. Consent, competence, and confidentiality. BMJ. 2005;330(7487):353–6. doi: http://dx.doi.org/10.1136/bmj.330.7487.353. PubMed.

23 World Health Organization. Children's rights in primary health care. Assessment and improvement Tool for Children and Adolescents aged 12-18. Copenhagen: World Health Organization; 2015. 50 pp.

24 United Nation General Assembly. United Nation Convention on the Rights of the Child. New York: United Nation General Assembly; 1990.

25 Caldwell JC, Caldwell P, Caldwell BK, Pieris I. The construction of adolescence in a changing world: implications for sexuality, reproduction, and marriage. Stud Fam Plann. 1998;29(2):137–53. doi: http://dx.doi.org/10.2307/172155. PubMed.

26 Kao TS, Guthrie B, Loveland-Cherry C, Caldwell CH. Cross-cultural variations in adolescents' perceived maternal expectancy and sexual initiation. J Transcult Nurs. 2012;23(4):377–88. doi: http://dx.doi.org/10.1177/1043659612452669. PubMed.

27 Steinberg L. Cognitive and affective development in adolescence. Trends Cogn Sci. 2005;9(2):69–74. doi: http://dx.doi.org/10.1016/j.tics.2004.12.005. PubMed.

28 Zdunek K, Alma M, Van Til J, et al. Listening to Young People. In: Blair M, Rigny, M, Alexander, D, ed. Issues and opportunities in primary health care for children in Europe. Bingley, UK: Emerald Publishing Limited; 2019. pp 55–76.

29 Council of Europe. Council of Europe guidelines on child-friendly health care. Strasbourg: Council of Europe; 2011. 20 pp.

30 Griffith R, Tengnah C. Assessing children's competence to consent to treatment. Br J Community Nurs. 2012;17(2):87–90. doi: http://dx.doi.org/10.12968/bjcn.2012.17.2.87. PubMed.

31 Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, van Goudoever JB, et al. Key factors in children's competence to consent to clinical research. BMC Med Ethics. 2015;16(1):74. doi: http://dx.doi.org/10.1186/s12910-015-0066-0. PubMed.

32 Lamont S, Jeon YH, Chiarella M. Assessing patient capacity to consent to treatment: an integrative review of instruments and tools. J Clin Nurs. 2013;22(17-18):2387–403. doi: http://dx.doi.org/10.1111/jocn.12215. PubMed.

33 Larcher V, Hutchinson A. How should paediatricians assess Gillick competence? Arch Dis Child. 2010;95(4):307–11. doi: http://dx.doi.org/10.1136/adc.2008.148676. PubMed.

34 Hein IM, De Vries MC, Troost PW, Meynen G, Van Goudoever JB, Lindauer RJ. Informed consent instead of assent is appropriate in children

from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research. BMC Med Ethics. 2015;16(1):76. doi: http://dx.doi.org/10.1186/s12910-015-0067-z. PubMed.

35 Stevens-Simon C. Assent in pediatric research. Pediatrics. 2006;118(4):1800–1, author reply 1801. doi: http://dx.doi.org/10.1542/peds.2006-1577. PubMed.

36 Hein IM, Troost PW, Lindeboom R, et al. Assesing children's competence to consent to treatment. In: AHein I, ed. Children's competence to consent to medical treatment or research. Amsterdam: Amsterdam University Press; 2015. pp 91–101.

37 Goldenring JM, Rosen D. Getting into adolescent heads: an essential update. Contemp Pediatr. 2004;21(4):64–80.

38 Larcher V. Developing guidance for checking pregnancy status in adolescent girls before surgical, radiological or other procedures. Arch Dis Child. 2012;97(10):857–60. doi: http://dx.doi.org/10.1136/archdischild-2012-302016. PubMed.

39 Zdunek K, Rigby M, Deshpande S, et al. Child Centricity and Children's Rights. In: Blair M, Rigny, M, Alexander, D, ed. Issues and opportunities in primary health care for children in Europe. Bingley, UK: Emerald Publishing Limited; 2019. p 77–98.

40 Burke TM, Abramovitch R, Zlotkin S. Children's understanding of the risks and benefits associated with research. J Med Ethics. 2005;31(12):715–20. doi: http://dx.doi.org/10.1136/jme.2003.003228. PubMed.

41 Gibson BE, Stasiulis E, Gutfreund S, McDonald M, Dade L. Assessment of children's capacity to consent for research: a descriptive qualitative study of researchers' practices. J Med Ethics. 2011;37(8):504–9. doi: http://dx.doi.org/10.1136/jme.2010.040097. PubMed.

42 Mack JW, Joffe S. Communicating about prognosis: ethical responsibilities of pediatricians and parents. Pediatrics. 2014;133(Suppl 1):S24–30. doi: http://dx.doi.org/10.1542/peds.2013-3608E. PubMed.

43 Massimo LM, Wiley TJ, Casari EF. From informed consent to shared consent: a developing process in paediatric oncology. Lancet Oncol. 2004;5(6):384–7. doi: http://dx.doi.org/10.1016/S1470-2045(04)01496-2. PubMed.

44 Steinberg L. Does recent research on adolescent brain development inform the mature minor doctrine? J Med Philos. 2013;38(3):256–67. doi: http://dx.doi.org/10.1093/jmp/jht017. PubMed.

45 Jaccard J, Levitz N. Counseling adolescents about contraception: towards the development of an evidence-based protocol for contraceptive counselors. J Adolesc Health. 2013;52(4, Suppl):S6–13. doi: http://dx.doi.org/10.1016/j.jadohealth.2013.01.018. PubMed.

46 Diserens C, Quach A, Mathevet P, Ballabeni P, Jacot-Guillarmod M. Adolescents' contraception continuation in Switzerland: a prospective observational study. Swiss Med Wkly. 2017;147:w14504. doi: http://dx.doi.org/10.4414/smw.2017.14504. PubMed.

47 Jacot-Guillarmod M, Diserens C. Contraception chez les adolescentes. Swiss Medical Forum. 2019;19(21–22):354–60. doi: http://dx.doi.org/10.4414/smf.2019.08067.

48 Pienkowski C, Cartault A. Contraception de l'adolescente. RPC Contraception CNGOF [Contraception for adolescent : CNGOF Contraception guidelines]. Gynécol Obstét Fertil Sénol. 2018;46(12):858–64. doi: http://dx.doi.org/10.1016/j.gofs.2018.10.034. PubMed.

49 Coles CB, Shubkin CD. Effective, recommended, underutilized: a review of the literature on barriers to adolescent usage of long-acting reversible contraceptive methods. Curr Opin Pediatr. 2018;30(5):683–8. doi: http://dx.doi.org/10.1097/MOP.0000000000000663. PubMed.

50 Clinical Trial Facilitating Group CTFG. Recommendations related to contraception and pregnancy testing in clinical trials. In: Agency EM, ed. Langen, Germany: Clinical Trial Facilitating Group CTFG; 2014. 13 pp.

51 Cook RJ, Erdman JN, Dickens BM. Respecting adolescents' confidentiality and reproductive and sexual choices. Int J Gynaecol Obstet. 2007;98(2):182–7. doi: http://dx.doi.org/10.1016/j.ijgo.2007.04.018. PubMed.

52 Narring F. Adolescent Pregnancy in Switzerland. In: Springer, ed. International Handbook of Adolescent Pregnancy. Heidelberg: Springer; 2014. pp 599–604.

53 Cherry A, Dillon ME. International Handbook on Adolescent Pregnancy. New York: Springer; 2014.

54 Michaud PA, Jansen D, Schrier L, Vervoort J, Visser A, Dembiński Ł. An exploratory survey on the state of training in adolescent medicine and health in 36 European countries. Eur J Pediatr. 2019;178(10):1559–65. doi: http://dx.doi.org/10.1007/s00431-019-03445-1. PubMed.