

hCG Testing to Determine Outcome after Medical Abortion: A Review

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Abstract

Introduction:

Results:

Conclusion:

Keywords: hCG; Medical abortion follow-up; Low-sensitivity urine hCG test

Introduction

Medical abortion using mifepristone in combination with misoprostol is known to be effective and safe [1]. But routine follow-up is necessary to assess treatment outcomes and to exclude on-going pregnancy [2]. Moreover, a follow-up visit is legally mandatory in many countries.

To facilitate follow-up, remote techniques using urinary Human Chorionic Gonadotropin (hCG) testing have been developed in recent years.

The use of Ultrasonography (US) at follow-up to assess medical abortion outcome is rapid and reliable if done by a qualified provider and provided the pregnancy has been visualised on ultrasound prior to treatment. For women, the disadvantage of US is an additional clinic visit, leading to reduced acceptability of medical abortion. This approach may also add costs for the woman or the health care provider. In addition, ultrasound findings alone, such as diameter of the uterine cavity, do not indicate a need for surgical intervention and interpretation depends on provider experience [3-5]. Therefore, other ways to reliably diagnose success or failure of medical abortion were searched and are currently under investigation.

The follow-up visit is often the time for contraception counselling. However, this should take place before initiating medical abortion, because women can ovulate 8-14 days after treatment. If they want to prevent subsequent unwanted pregnancy, they should start reliable contraception immediately after medical abortion, before the follow-up visit [6,7]. Postponing contraception provision increases the risk

of subsequent unplanned pregnancy. All methods of contraception, including Intra-Uterine Devices (IUDs) and hormonal contraceptives, can be initiated immediately after medical abortion [1]. To prevent unnecessary visits to the clinic, Implants should be placed at the time of mifepristone treatment to allow a quick start for this reversible contraceptive method [8].

In addition, treatment of potential medical abortion complications should not be delayed until a scheduled follow-up. Some women with an on-going pregnancy after medical abortion may not feel any pregnancy-related symptoms and therefore would miss an on-going pregnancy without using US or hCG [9]. This means that determining the outcome of medical abortion based on self-perception or by history-taking is inadequate [9]. A diagnostic tool like hCG is needed to reliably diagnose medical abortion outcomes, especially when women do not attend follow-up visits.

Using serum hCG testing to diagnose outcome is highly reliable but adds an invasive blood test and requires an extra visit. Urinary hCG testing has therefore been proposed as a more practical alternative, especially with newly developed low-sensitivity tests that give a

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positive result above a threshold of 500-1000 U/L. No comprehensive information on that subject, including the more recent techniques, is available.

This systematic review examined the evidence regarding serum and urine hCG testing for determining medical abortion outcome and how these tests can be part of follow-up management of medical abortion up to 63 days of gestation.

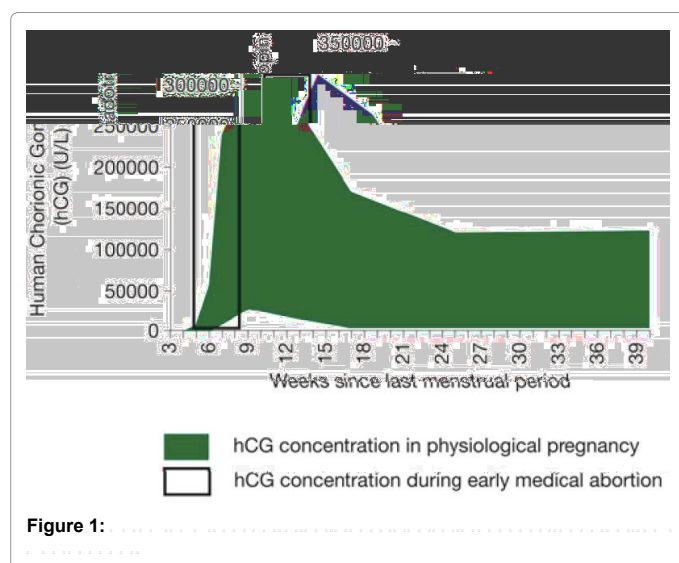
Method and Materials

An extensive literature search was performed using MedLine, with key words “hCG” AND “abortion” and “abortion” AND “follow-up”, to identify publications in English from 2003 to 2016 that provided information on serum and urinary hCG testing up to 63 days medical abortion and during follow-up. All articles with an English abstract were reviewed. Titles and abstracts were used to identify studies related to gestations up to 63 days and information regarding gestations above 9 weeks was excluded. In addition to medical abortion studies, studies describing hCG changes during pregnancy and after the end of pregnancy, including causes other than medical abortion, were included. A total of 910 references were found, of which 35 clearly fit the topic and were included. These papers provided information regarding hCG course during pregnancy and/or hCG testing for medical abortion follow-up (Table 1).

Results

The course of hCG during pregnancy[†] and after medical abortion

During pregnancy, hCG values differ significantly. Levels are zero in non-pregnant women, show pronounced changes over time like doubling every 48-72 h in early pregnancy, peak at 8-11 weeks of gestation at levels around 200,000 U/L and then decline for the rest of the pregnancy [10]. In early pregnancy, urinary hCG levels increase daily by approximately 50% [11]. But huge individual variations make it impossible to date gestational age based on hCG levels. Similarly, it is not possible to diagnose successful abortion with a single test at follow-up within two weeks after treatment. This explains why two tests are needed to give a rapid result of the abortion, one at baseline and one at follow-up to determine the outcome (Figure 1).



The decline in serum hCG following pregnancy termination is steep initially, but low levels can remain up to 4-6 weeks. An hCG decrease in the days following medical abortion is described in different studies [12-14]. There is no consensus regarding the threshold of hCG at follow-up in terms of percent of the initial value that would indicate a successful abortion. Different opinions also exist on the speed of decrease of hCG following medical abortion. The rate was thought by some authors to depend on the initial hCG level, with a more rapid decline associated with a higher baseline concentration before treatment [12]. Following medical abortion using mifepristone and misoprostol, hCG declined by $70.5 \pm 8.8\%$ in the 24 h following misoprostol, with no correlation between the percentage decline within 24 h and the peak hCG level measured prior to misoprostol administration [6]. Further, the reported rate of decline ranged widely from 21% to 35% at 2 days and 60% to 84% at 7 days, depending on initial hCG value or with at least a 90% decline in 95% of women at 5 days [12,14].

Serum hCG testing to determine outcome of medical abortion

In a prospective observational study, Fiala et al. compared the usefulness of hCG measurement and ultrasound examination before and after medical abortion to determine treatment outcome [3]. The study included 217 women who underwent medical termination of pregnancy up to 49 days of amenorrhea using mifepristone and misoprostol. Ultrasound examination and a serum hCG test were performed before treatment and at follow-up (D6-D18). The hCG levels at follow-up dropped to a mean of 3% (± 3) of the value before treatment, ranging from 1 to 44% of the initial value in cases of successful abortion. When 20% of the initial hCG value was used as a cut-off, a positive predictive value for successful expulsion of 0.995 was obtained. If the reduction of the hCG level was less than 80%, the negative predictive value was 0.5 and further evaluation was needed to confirm the outcome of treatment.

Further studies confirmed these results. In a retrospective study of 172 women who underwent medical abortion for pregnancy up to 63 days, the rate of decrease in hCG from baseline to 7 days was above 20% in only 4/91 women with successful abortions [15]. A prospective study described a decrease of 99% in serum hCG at 15-71 days in 99% of 255 women who underwent abortion up to 63 days [16].

Another prospective observational study of 254 women who underwent medical abortion from 63 to 90 days showed a decline in hCG above 97.5% in women with successful termination [17].

In a prospective comparative study of 144 women with treatment for missed abortion or blighted ovum and a gestational age below 12 weeks, serum hCG testing was considered as effective as ultrasound in confirming medically-induced abortion 2 and 4 weeks after expulsion, with a kappa correlation coefficient of 0.327 [18].

A prospective, controlled and randomized study of 376 women who underwent medical abortion up to 63 days showed no significant difference in the low-level rate of unplanned interventions and visits between arms -8.2% in the hCG arm vs 6.6% in the ultrasound arm at 2 weeks [19].

The use of serum hCG testing did not significantly decrease adherence to follow-up visits. In a retrospective chart review of 885 women who underwent medical abortion, the rates of loss to follow-up were 23% in women choosing follow-up via in-office ultrasound assessment and 34% in women choosing hCG testing [20]. However, the women who chose hCG testing were inherently less likely to follow up. There was no difference between groups in the rate of loss to follow-

Reference	Study	Objective	Country	Date	Medical Abortion	n	Test	Pre-Abortion Test	Post-Abortion Test	Assessment	Results
1. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
2. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
3. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
4. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
5. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
6. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
7. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
8. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
9. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]
10. [Reference]	[Study]	[Objective]	[Country]	[Date]	[Medical Abortion]	[n]	[Test]	[Pre-Abortion Test]	[Post-Abortion Test]	[Assessment]	[Results]

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<p>1. The first part of the paper discusses the importance of early diagnosis and treatment of infectious diseases in children, particularly in developing countries. It highlights the challenges faced by these regions, such as limited access to healthcare and high rates of malnutrition, which can exacerbate the severity of infections.</p>	<p>2. The second part of the paper reviews the current state of research on various infectious agents, including bacteria, viruses, and parasites. It discusses the latest findings on their pathogenesis, transmission, and clinical manifestations, as well as the effectiveness of existing diagnostic and therapeutic interventions.</p>	<p>3. The third part of the paper focuses on the role of the immune system in the response to infections. It explores how the immune system recognizes and eliminates pathogens, and how this process can be modulated by various factors, including genetics and environmental influences.</p>	<p>4. The fourth part of the paper discusses the importance of vaccination in the prevention of infectious diseases. It reviews the development and implementation of various vaccines, and the impact of vaccination programs on public health.</p>	<p>5. The fifth part of the paper discusses the role of the microbiome in the development and regulation of the immune system. It explores how the composition and function of the microbiome can influence the host's response to infections, and how this knowledge can be used to develop new therapeutic strategies.</p>	<p>6. The sixth part of the paper discusses the role of the gut in the response to infections. It explores how the gut microbiome and the gut-associated lymphoid tissue (GALT) interact to provide a first line of defense against pathogens that enter the body through the oral route.</p>	<p>7. The seventh part of the paper discusses the role of the skin in the response to infections. It explores how the skin acts as a physical barrier to pathogens, and how the skin's immune system can recognize and respond to infections that breach this barrier.</p>	<p>8. The eighth part of the paper discusses the role of the respiratory system in the response to infections. It explores how the respiratory tract is a major site of infection, and how the immune system can respond to pathogens that enter through the nose and mouth.</p>	<p>9. The ninth part of the paper discusses the role of the nervous system in the response to infections. It explores how the nervous system can be affected by various infectious agents, and how this can lead to neurological complications.</p>	<p>10. The tenth part of the paper discusses the role of the cardiovascular system in the response to infections. It explores how the cardiovascular system can be affected by various infectious agents, and how this can lead to cardiovascular complications.</p>	<p>11. The eleventh part of the paper discusses the role of the reproductive system in the response to infections. It explores how the reproductive system can be affected by various infectious agents, and how this can lead to reproductive complications.</p>	<p>12. The twelfth part of the paper discusses the role of the endocrine system in the response to infections. It explores how the endocrine system can be affected by various infectious agents, and how this can lead to endocrine complications.</p>	<p>13. The thirteenth part of the paper discusses the role of the musculoskeletal system in the response to infections. It explores how the musculoskeletal system can be affected by various infectious agents, and how this can lead to musculoskeletal complications.</p>	<p>14. The fourteenth part of the paper discusses the role of the integumentary system in the response to infections. It explores how the integumentary system can be affected by various infectious agents, and how this can lead to integumentary complications.</p>	<p>15. The fifteenth part of the paper discusses the role of the sensory system in the response to infections. It explores how the sensory system can be affected by various infectious agents, and how this can lead to sensory complications.</p>
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<p>1. The first part of the paper discusses the importance of early diagnosis and treatment of infectious diseases in children. It highlights the role of the pediatrician in identifying and managing these conditions, emphasizing the need for a thorough history and physical examination.</p>	<p>2. The second part of the paper focuses on the clinical presentation and diagnostic challenges of infectious diseases in children. It discusses the importance of recognizing atypical presentations and the role of laboratory investigations in confirming the diagnosis.</p>	<p>3. The third part of the paper discusses the management of infectious diseases in children, including the use of antibiotics, antivirals, and vaccines. It emphasizes the importance of adherence to treatment and the role of the pediatrician in monitoring the response to therapy.</p>	<p>4. The fourth part of the paper discusses the importance of infection control measures in the pediatric setting. It highlights the role of the pediatrician in educating parents and staff about proper hygiene and the use of personal protective equipment.</p>	<p>5. The fifth part of the paper discusses the importance of research in the field of pediatric infectious diseases. It highlights the need for further studies to improve the diagnosis and management of these conditions and to develop new vaccines and treatments.</p>	<p>6. The sixth part of the paper discusses the importance of collaboration between pediatricians and other healthcare professionals in the management of infectious diseases in children. It highlights the role of the pediatrician in coordinating care and ensuring that the child receives the best possible outcome.</p>	<p>7. The seventh part of the paper discusses the importance of patient and family education in the management of infectious diseases in children. It highlights the role of the pediatrician in providing clear and concise information to parents and patients about the condition and the treatment plan.</p>	<p>8. The eighth part of the paper discusses the importance of ongoing education and professional development for pediatricians in the field of infectious diseases. It highlights the need for pediatricians to stay up-to-date on the latest research and clinical practice guidelines.</p>	<p>9. The ninth part of the paper discusses the importance of quality improvement initiatives in the management of infectious diseases in children. It highlights the role of the pediatrician in identifying areas for improvement and implementing changes to enhance the quality of care.</p>	<p>10. The tenth part of the paper discusses the importance of research in the field of pediatric infectious diseases. It highlights the need for further studies to improve the diagnosis and management of these conditions and to develop new vaccines and treatments.</p>
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Abbreviations:

Table 1:

up in another prospective study comparing the adherence to follow-up between standard in-clinic and remote follow-up in 129 women who underwent medical abortion up to 49 days of gestation (rate of loss to follow-up: 28% for remote vs 23% for standard follow-up) [21].

Urine pregnancy test (urine hCG test) and medical abortion

The concordance between urine and serum beta-hCG measurement was demonstrated in multiple studies.

Urine beta-hCG testing (Orchid Biomedical System) followed by serum testing in 97 women up to 3 weeks after medical abortion (or during normal pregnancies) demonstrated good sensitivity (89%) and specificity (72%) of the urine test for identifying individuals with a serum beta-hCG >1000 U/L [22]. In another prospective study of 322 women who underwent medical abortion up to 63 days, the concordance between urine (low sensitivity urine pregnancy test hCG Duo 5-1000) and serum beta-hCG levels was 94.5% [23].

Urine pregnancy tests have good sensitivity and good specificity to detect outcome of medical abortion up to 63 days [1,24-27]. Therefore, low-sensitivity hCG tests were developed. In a prospective observational study of 3054 women who underwent medical abortion up to 63 days, a low-sensitivity urine pregnancy test combined with women's self-assessment and a non-sonographic clinical evaluation was as effective as US in identifying all women with on-going pregnancies at follow-up 7 to 14 days after treatment [28].

Self-assessment using urine pregnancy test combined with other measures

Different self-assessment protocols that women can do at home were evaluated using various urine tests. The objective was to decrease the high loss to follow-up to 18 to 30% when women are asked to return for a follow-up visit and to determine medical abortion outcomes while individualising follow-up according to women's preference [22]. Low-sensitivity urinary pregnancy tests have various thresholds of hCG ranging from 500 to 2000 mIU/ml, while high-sensitivity urinary pregnancy tests can detect hCG levels as low as 5 mIU/ml.

The feasibility of protocols combining a urine pregnancy test and telephone follow-up was confirmed in multiple studies. A protocol required a phone call 7 days after mifepristone administration, followed by US if the woman or clinician thought the pregnancy was not expelled. Otherwise, cases were followed by a high-sensitivity urine pregnancy test 30 days after mifepristone and a phone call 3 days after the urinary test. It led to 97% complete follow-up in 139 women undergoing medical abortion up to 63 days in a study in 2400 women, the use of a home semi-quantitative urine pregnancy test in combination with a standardized checklist over the phone led to a 98% rate of follow-up [29]. This compared to a 100% follow-up rate in women attending clinical examination in combination with optional US 2 weeks after mifepristone for medical abortion up to 63 days [30]. The adherence to scheduled follow-up was 92% in women who took a low-sensitivity urine pregnancy test at home in combination with a home visit or phone. This compared to a 78% follow-up rate for women coming to a clinic 10 to 14 days after medical abortion for a bimanual pelvic examination and low-sensitivity urine pregnancy test in a randomized study of 731 women undergoing medical abortion up to 63 days [31,32]. A prospective, comparative, randomized study compared clinical assessment with self-assessment of abortion outcome in 924 women who underwent medical abortion up to 63 days. Follow-up was performed 1 to 3 weeks after abortion. No women in the routine follow-up group had undetected continuing pregnancies in the second

trimester, versus 3 (0.7%) in the self-assessment group. However, self-assessment was non-inferior to routine follow-up [33].

The usefulness of a remote/at home follow-up was also assessed in a prospective study comparing the rate of follow-up in 999 women undergoing medical abortion up to 63 days [34]. Women were randomized either to: 1) a "clinic-based" group with US 1 week after mifepristone administration or a high-sensitivity urine pregnancy test performed at 3 weeks and a telephone call with clinic staff if the woman could not attend the 1-week follow-up visit or 2) to a "remote follow-up" group using a low-sensitivity pregnancy test and a standardized questionnaire administered by a non-clinical call centre operator by phone, text message or internet 2 weeks after treatment. The rate of follow-up was 69% for remote follow-up and 73% for clinic-based follow-up, but in the latter group, most failed to return for their scheduled US and were followed by phone (83%). This high level of follow-up was also confirmed in a retrospective analysis of 176 women who underwent medical abortion up to 63 days with a rate of lost to follow-up of 5.6% for phone follow-up in combination with urine pregnancy test within 4 weeks after medical abortion [35].

The sensitivity and specificity of a remote protocol using a low-sensitivity urine pregnancy test in combination with telephone follow-up, were high, respectively 75% to 100% and 85 to 88% at 2 weeks after medical abortion up to 63 days [31,36-38].

During clinical studies, 81 to 85% of women did a home urine pregnancy test without waiting for the planned telephone follow-up [28,35]. Based on this finding, a study was conducted where women could do a urine pregnancy test at home in combination with self-assessment. Women were asked to contact the abortion service in case of a positive or invalid test and in case of predefined signs and symptoms. Results were assessed in 1726 women undergoing medical abortion up to 63 days [39]. A total of 96% of women chose self-assessment and 6% of those phoned the service. Eight on-going pregnancies occurred (0.5%, 95% confidence interval 0.2-0.9%), with 4 detected within 4 weeks of treatment and the remainder not detected until one or more missed menses after the procedure. In another prospective study, the self-assessment was provided either as a paper document or as an automated interactive questionnaire on women's mobile phones [40]. There was a good prediction of complete procedure in 71% of women who used the mobile phone assessment and 91% of those who sent a paper assessment.

A 2011 Cochrane meta-analysis of 8 studies looked at alternative follow-up modalities after first-trimester medication abortion to diagnose on-going pregnancy or retained gestational sac [9]. The sensitivity, specificity, positive predictive value and negative predictive value were calculated and compared with ultrasound or clinician examination. The most promising follow-up modalities included serum hCG measurements, low sensitivity urine pregnancy test combined with a standardized assessment of women's symptoms and standardized telephone consultation (perhaps followed by high sensitivity urine pregnancy test). These follow-up modalities had sensitivities of 90% and negative predictive values of 99% and resulted in a proportion of "screen-positives" of 33%.

Discussion

The aim of this review was to describe the use of hCG testing for medical abortion outcomes. More specifically, it explored urinary hCG testing using low-sensitivity tests that could facilitate self-assessment follow-up, improve access to medical abortion in areas where there

is no US access, decrease the rate of unnecessary surgery in case of misinterpretation of US, reduce the time interval until outcome can be determined and increase women's autonomy in the abortion process.

Thirty-five studies were identified, of which 20 were related to urinary hCG testing, either alone or in combination with self-assessment. These studies illustrated the course of historic development of current tests, including the initial use of serum hCG testing, followed by the use of high-sensitivity urinary pregnancy tests and finally, low-sensitivity urinary hCG testing. This may explain the differences found in the results of these studies.

This review confirmed that serum hCG testing allows for determination of medical abortion outcomes. The good sensitivity and good specificity of urine hCG tests to detect outcomes up to 63 days was also demonstrated. However, the high sensitivity to detect hCG and slow reduction of hCG in the human body after a successful termination of pregnancy implies that a very long interval is necessary before a normal hCG test would become negative, i.e. 4-6 weeks. This could lead to a delay in the diagnosis of on-going pregnancy as well as stress for the woman. New, low-sensitivity urine hCG tests have therefore been developed to allow for earlier assessment.

To increase acceptability and reduce unnecessary surgical and medical interventions after medical abortion, the current follow-up protocols after medical termination of pregnancy should be revised. Current follow-up protocols, sometimes even legally mandatory, require the woman to come back to the clinic for an additional visit and/or for US. The high loss to follow-up rate may be due to the woman's conviction that the pregnancy has ended combined with a good health feeling. Consequently, many women see no need to spend time and energy to see a doctor. Moreover, in countries where transportation is difficult, interest in self-assessment using urinary hCG testing was demonstrated [31].

Of the recently proposed follow-up protocols, most do not recommend a clinic visit. Follow-up may consist of remote assessment, which may include clinical symptom assessment as well as hCG testing using low sensitivity urine pregnancy test. Some use urine pregnancy testing combined with telephone follow-up. The latter could be replaced with written information given to patients as there is nothing that could be asked exclusively during a telephone by another person instead of written information handed over to the patient. A recent study from Scotland found that when given the option, most women who plan to go home to expel a pregnancy following an early medical abortion choose not to receive a phone call from the abortion service [41].

Relying solely on hCG testing at early follow-up in medical abortion is challenging because of huge individual hCG variations during the first trimester. A reliable diagnosis based on a single test becomes even more difficult because of the variation of hCG decline after successful medical abortion. Therefore, a baseline hCG test at the beginning of treatment is necessary to allow comparison with the follow-up result. However, the new low-sensitivity tests allow use of a single test if an intrauterine pregnancy has been diagnosed at the beginning of treatment. Another benefit of these new tests is their ease of use for all women regardless of education or literacy level.

One of the limitations of this review is the absence of information regarding surgical management of medical abortion outcomes in the presence or absence of hCG testing. This does not allow for any comparison between various follow-up techniques. In addition, concomitant parameters including the quality of medical care, the psychological and relational dimensions of the woman's request and

the woman's feelings during abortion should also be taken into account when comparing various follow-up techniques.

Conclusions

The different protocols described in this review, including serum hCG testing, urinary hCG testing, paper questionnaire for self-assessment and mobile phone questionnaire, allow practitioners to individualise and personalise medical abortion follow-up without impairing safety, as long as contraceptive counselling is undertaken before initiation of medical abortion. The use of low-sensitivity urine hCG testing improves follow up, as it saves women from unnecessary clinic visits and shortens the time interval to obtain accurate results.

Declarations

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References

