Identify, appraise and individualize: clinical practice and prediction models in recurrent pregnancy loss

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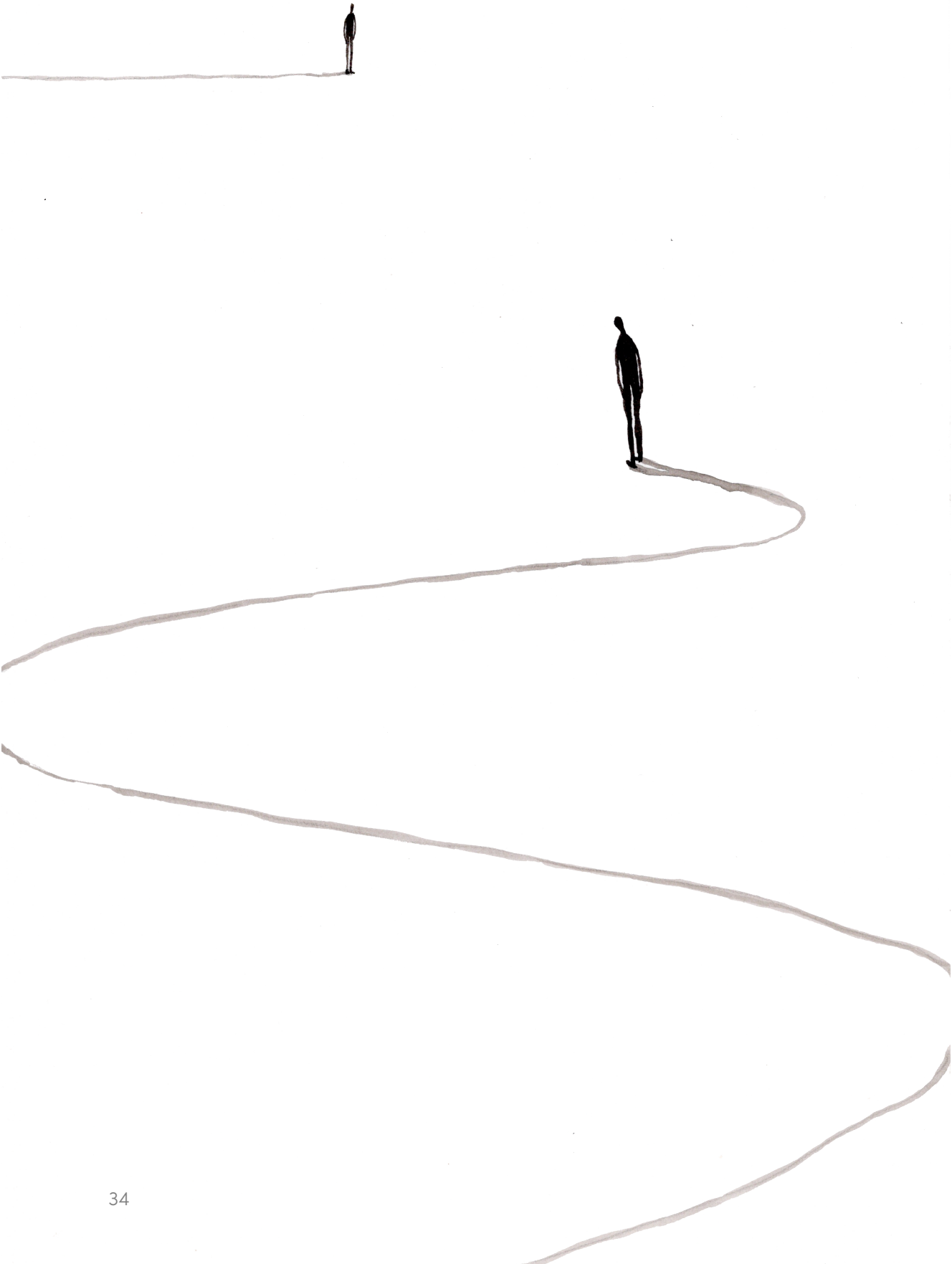

PART I

GUIDELINES AND IMPLEMENTATION

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CHAPTER 2

PORTRAYING CLINICAL VARIATIONS: RECURRENT PREGNANCY LOSS GUIDELINE

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Adapted from Nederlands Tijdschrift voor Obstetrie en Gynaecologie, 2017

INTRODUCTION

In the "portraying clinical variations" column, differences and similarities between various local and regional protocols and national guidelines of a common disease are investigated. For this a sample of academic and non-academic protocols, geographically dispersed throughout the Netherlands, is used. This column is written by two obstetrics & gynaecology residents, with the aim of discussing the unification of local and regional protocols in accordance with national guidelines.

In prior editions of this protocol discussion, the protocols gestational diabetes and hypertensive disorders in pregnancy have been discussed. This third part of the series discusses the recurrent pregnancy loss (RPL) guideline (1, 2). Seven local protocols will be compared to each other, as well as to the national guideline (3). Besides the seven approached hospitals, one academic and one non-academic hospital indicated that they work with the national guideline without local adjustments.

DEFINITION OF RPL

RPL is defined as the objectified loss of two pregnancies of a couple. The losses do not have to be consecutive. Ectopic pregnancies and molar pregnancies are excluded from the definition.

NATIONAL GUIDELINE

The Dutch national guideline of the Dutch Society of Obstetrics and Gynaecology (NVOG) dates from 2007. This guideline discusses the probable risk factors of RPL. Furthermore, it provides an overview of recommendations regarding investigations and therapy, based on available literature. In summary, there are no recommended drug treatments (except for antiphospholipid syndrome (APS)); lifestyle recommendations are the main treatment options.

RPL

Approximately 15% of pregnant women experience a pregnancy loss. Only 3% of pregnant women experience the loss of two pregnancies, and 0.4 – 1 percent experience the loss of three pregnancies. There are two key concerns in couples with RPL: the cause of RPL and the chance of recurrence. In a first pregnancy, the chance of a pregnancy loss in the

following pregnancy remains 15% (depending on a maternal age), but rises to 17-31% after two pregnancy losses and up to 46% after three pregnancy losses. For that reason, investigations after two pregnancy losses are recommended (4-6). Unfortunately, in up to 50% of couples no cause can be identified (7). The chance of an ongoing pregnancy after RPL depends on maternal age, and the number of preceding pregnancy losses. In general, the chances of a successful pregnancy are higher than a negative outcome. The chance of an ongoing pregnancy beyond 12 weeks is approximately 75% in a next pregnancy (8).

GENERAL IMPRESSIONS OF GUIDELINES

Besides the fact that protocols should be practical and effective in daily clinical practice, there are a couple of other points to assess the general quality of the guidelines.

1. Is the intended population clearly defined and complete?

2. Are the recommendations for diagnostics, treatment and follow-up clear? In other words: not highly subject to individual interpretation or free of interpretation?

3. Do the given recommendations match the best available evidence and/or national guideline? Are there references to used sources?

4. Does the protocol only apply at the clinic or is it a regional or transmural protocol?

Mentioned in table 1 are the protocols from different (anonymised) academic and non-academic hospitals. Except protocol P3, all protocols mention their definition for RPL and all protocols clearly define the targeted population. The protocols vary in terms of information provision, some of the protocols provide brief background information and touch briefly upon investigations and therapy. Other protocols contain extensive background information and specify per probable cause the therapeutic options. The Dutch guideline is seen as a guide by all protocols, there are however a few differences. These differences will be explored below. The protocols relate to a specific clinic and are not transmural. Protocols U2 and P4 provide a thorough reference list, U1, P1, P2 and P3 only refer to the NVOG guideline.

RESULTS

TERMINOLOGY

In 2005, the Special Interest Group for Early Pregnancy of the European Society for Human Reproduction and Embryology (ESHRE) suggested to change the European nomenclature of young pregnancies in the English language (9). Reason was that the old terminology dated from before the ultrasound era. Furthermore, different terms were being used in describing the same phenomenon, which could lead to confusion. In 2008, the NVOG suggested to replace "habitual abortion" with "recurrent pregnancy loss" to prevent confusion in patients and in medical staff (10). Except for protocol P3, the definition of RPL is mentioned in each protocol and is generally speaking in accordance to the NVOG definition.

DIAGNOSTIC DECISION AID

One protocol (P3) refers to the decision aid found on the Freya website. This program is based on the Dutch guideline and provides medical staff the ability to determine which investigations should be performed for each RPL couple (11).

RISK FACTORS

Five of the seven protocols contain information regarding risk factors. In the remaining two protocols (U3 and P3), risk factors are mentioned in the paragraphs describing treatment options. What stands out here is the mentioning of M. Wilson as a risk factor in protocol P2, while this risk factor is not mentioned by the NVOG. M. Wilson is a very rare, autosomal recessive disease occurring in 1:30.000 live births (12). Subfertility is followed by menstrual abnormalities caused by liver cirrhosis. Spontaneous pregnancies in untreated disease, will result in pregnancy losses through the excessive copper amounts in the uterus (13-15). The treatment of this disease is mentioned in the treatment paragraph of this protocol, as well as in protocol P1. The latter protocol however did not mention this disease as a risk factor.

INVESTIGATIONS

GENERAL

The protocols state in varying manner which components of the patient history are important. Four protocols (U1, U2, U3 and P2) clearly state what questions should be included when obtaining a patient's history. Other protocols do not mention this, or mention it very briefly.

GENETICS

Karyotyping is being performed when a risk assessment based on age and family history provides reason to do so. The chance of structural chromosomal abnormalities in couples with two or more pregnancy losses is key here. According to the NVOG, it is advised to perform karyotyping in women when 34 years of age and younger at time of the second pregnancy loss, regardless of the total number of pregnancy losses is. Between the age of 34 and 39 at time of the second pregnancy loss, it is advised to perform karyotyping depending on family history, total number of pregnancy losses and maternal age. In women above 39 years old, it is advised not to perform genetic testing. All protocols mention karyotyping, only one protocol (P2) does not refer to the risk assessment table available in the NVOG guideline. The protocol of an academic hospital (U3) shows that karyotyping is also performed in case of a patient history with genetic abnormalities, or family genetic abnormalities.

It is known that 50% of early pregnancy losses are caused by chromosomal abnormalities of the foetus. Numerical abnormalities have no increased risk for a new pregnancy, karyotyping thus has no clinical consequences. The NVOG advises not to perform genetical testing on the pregnancy product. Protocol U1 mentions that this could be performed in case of scientific research.

THROMBOPHILIA

Antithrombin III, Factor II, V Leiden and Protein C and S are investigated on indication in all hospitals. Protocol P2 does not mention that screening is performed in case of a patient history or family history of thrombophilia as mentioned by the NVOG. The screening performed by all hospitals largely matches each other. Only protocol U1 performs extensive coagulation testing in case of three pregnancy losses.

IMMUNOLOGY/ANTIPHOSPHOLIPID ANTIBODIES SYNDROME

These investigations are focused on detecting APS. Anticardiolipin antibodies (ACA) and Lupus antibodies (LAC) should be tested at least twelve weeks after the occurrence of a pregnancy loss, followed by a confirmation test also twelve weeks later. All of the protocols perform the investigations as mentioned by the NVOG. In four hospitals (U1, U2, P2 and P4) bèta-2-glycoprotein is also tested for. The protocols do not always mention what type of antibodies are tested for (IgG and IgM). There's a difference in the advice of the timing of testing for APS. This ranges from six to twelve weeks after pregnancy. Two of the seven protocols do not advice on repeating testing.

HYPERHOMOCYSTEINEMIA

The protocols use different investigational methods to assess hyperhomocysteinemia. These methods are: random homocysteine, fasting homocysteine and methionine load test. The methionine load test can be performed in patients where hyperhomocysteinemia is suspected, but fasting homocysteine is not outside normal values. All academical hospitals use random homocysteine measurement.

ENDOCRINOLOGY

Endocrinological investigations are not discussed in protocols P1, P2 and P3. The other protocols describe the measurement of thyroid function only in context of the T4LIFE study, for which TPO antibodies are also investigated, or in the context of a patient history suggesting thyroid disease. It is known that TPO antibody levels could increase the chance of pregnancy loss and preterm birth. The T4LIFE study investigates whether levothyroxine in patients with normal thyroid function but TPO antibodies and RPL increases the live birth rate (16).

ANATOMY

Ultrasound of the uterus is advised in 5 protocols (U1, U2, U3, P2 and P4). One academic protocol, U1, uses 3D ultrasonography only in case of suspicion of a uterine anomaly.

THERAPY

LIFESTYLE RECOMMENDATIONS

Protocols U1, U2, U3, P1 and P4 contain lifestyle recommendations according to the NVOG guideline. Protocol P4 also advises to reduce coffee and alcohol intake and to check the usage of medications. Protocol P2 does not specify the recommendations, protocol P4 only notes that weight loss should be advised. These recommendations are for all patients, independent of underlying disease.

ANTIPHOSPHOLIPID ANTIBODIES SYNDROME

Except for two protocols, APS treatment is as advised by the NVOG guideline: 75-80 mg aspirin preconceptionally until 36 weeks gestation in combination with low molecular weight heparin once daily from the detection of a foetal heartbeat. Protocol P2 advises 5000-E-heparin twice daily. Protocol P4 advises starting fraxiparin once there's a positive pregnancy instead of at the detection of foetal heartbeat. Academic protocol U1 refers to their own APS protocol.

The evidence and effectivity of the treatment described above is not of high quality. The NVOG refers to two systematic reviews and an RCT, concluding that the combination of heparin and aspirin reduce the chance of a pregnancy loss (17-19). The national antithrombotic guideline recommends considering this treatment regimen (20). A recent meta-analysis concludes that this treatment is not effective (21). Furthermore, it is concluded that aspirin without heparin results in negative outcomes. In other cohort studies this negative association between aspirin and the risk of pregnancy loss was already made (22).

The suggested mechanism described is that aspirin suppresses the biosynthesis of prostaglandin, which plays an important role in the implantation of the embryo. Regarding the order of starting aspirin and heparin, there is no recommendation described in scientific literature. Expert opinion advises to start with heparin at time of a positive pregnancy test, followed by aspirin at detection of a foetal heartbeat because of the assumption that heparin plays an immunological role in the implantation.

BALANCED CHROMOSOMAL ABNORMALITIES

In case of a balanced chromosomal abnormality, the three academic hospitals advise referring the couples to a geneticist. Protocols P1 and P3 do not describe a treatment proposal, in other protocols it is described that couples should be counselled and should be offered antenatal investigations in the following pregnancy. Four of the seven protocols mention the possibility of preimplantation genetic testing after IVF, as mentioned in the NVOG guideline.

SEPTATE UTERUS

Treatment of a uterine septum is being investigated in the TRUST study, which is an RCT investigating the effect of hysteroscopic resection of the septum on live birth rate (23). This study is mentioned in U1, U2 and P4

THROMBOPHILIA

In case of thrombophilia, U1 and U3 refer to the ALIFE-II study, which investigates the effect of low molecular weight heparin on the chance of a pregnancy loss in comparison with no treatment (24). The other protocols do not contain any treatment, based on the lack of evidence.

HYPERHOMOCYSTEINEMIA

The Dutch guideline recommends investigating folic acid, vitamin B6 and vitamin B12 in case of abnormal homocysteine levels. Homocysteine supplementation is recommended at low levels, after which homocysteine measurement should be repeated 6 weeks after supplementation. The Dutch guideline also suggests when trying to get pregnant could be considered responsible, and how to manage during and after pregnancy. This management is based on the Dutch Health Council (25). Two academic protocols and two non-academic protocols (U1, U2, P3 and P4) are mostly the same as the NVOG. The last academic protocol does not recommend anything regarding hyperhomocysteinemia treatment in a following pregnancy. The two other non-academic protocols touch very briefly upon folic acid and vitamin B6 supplementation.

MORBUS WILSON

M. Wilson or hepatolenticular degeneration usually results in neurological symptoms, psychiatric symptoms or symptoms of liver failure. RPL is

almost never a first symptom (26). Two non-academic hospitals mention the treatment of the disease, P1 with penicillamine or zinc and P2 with penicillamine. M. Wilson was not mentioned as risk factor in protocol P1. Penicillamine binds copper an excretes it through urine. Because of its side effects, trientine can be used (27). There are no trials comparing these two chelators.

UNEXPLAINED RPL

Two of the three academic protocols (U1 and U3) mention the practice of Tender Loving Care (TLC) in unexplained RPL. They offer weekly ultrasounds during pregnancy and offer psychological counselling. One non-academic hospital also mentions TLC options in unexplained RPL. Almost all protocols refer to the high success rates in a following pregnancy mentioned in the Dutch Guideline.

CONCLUSION

In this edition of "Portraying clinical Variations", seven protocols have been compared to each other and to the NVOG guideline. The differences between protocols were merely in the details of performed investigations. Not always the protocols mention when to perform what investigations. This could result in confusion for residents, as it is important for example for some investigations to be performed several weeks after a pregnancy. Descriptive information can be useful in making the choice for investigations understandable. In many hospitals, a specialist outpatient clinic for RPL couples is available. Most of the time, this clinic is run by a small team, it is of interest for the resident to be able to witness and participate in this consultation. It could also be that patients visit general outpatient clinics, with a history of two or more pregnancy losses. Knowledge of RPL protocols is of importance for the resident, as they could provide information regarding RPL for each couple. A well-designed guideline is desirable. Most of the guidelines are well designed, but some are obsolete, as they did not include the results of the Promise trial (28). This is also the case for the national guideline, which dates to 2007. It is therefore time to revise the guideline. There are however several studies that investigate outcomes in couples with RPL. Thus, it is sensible to wait for those results, after which a new version of the guideline could be developed.

TABLE 1 | RPL practice across academic and non-academic hospitals

	NVOG guideline	Academic Hospital U1	Academic Hospital U2	Academic Hospital U3
Terminology	Recurrent Pregnancy Loss	Recurrent Pregnancy Loss	Recurrent Pregnancy Loss	Recurrent Pregnancy Loss
Defining RPL	2 or more objectified pregnancy losses (could be non-consecutive)	Conform NVOG	Conform NVOG	Conform NVOG
Risk factors	- APS - Cytogenetic abnormalities - Embryonic factors - Endocrinologic - Hyperhomocysteinemia - Living habits - Maternal Age - Thrombophilia - Uterine factors	- Cytogenetic abnormalities - Endocrinologic factors (Anti-TPO, disturbed glucose balance) - High Maternal Age - Hyperhomocysteinemia - Living habits (smoking, obesity) - Clotting abnormalities (thrombophilia, APS) - Uterine factors	- Previous pregnancy losses - Endocrinologic factors - Genetic factors - Hematologic factors - Immunologic factors - Living Habits - Maternal age - Paternal factors - Uterine factors	- Not specified
Investigations				
General investigations	- BMI - Living habits	- BMI - Living habits - Extensive patient history	- BMI - Living habits	- BMI - Living habits - Extensive patient history
Genetics	- Karyotyping according to risk table - No genetical testing of foetal material	- Conform NVOG - Karyotyping of foetal material only in scientific research setting	- Conform NVOG	- Conform NVOG + - In case of family history of chromosomal abnormalities

Genetics (continued)				- Previous child with genetic abnormalities - In case of consanguinity
Thrombophilia	- Only in case of venous thromboembolic event in patient history and/or first-degree family with thrombophilia and venous thromboembolic event - Antithrombin III - Factor V Leiden - Factor II - Factor VIII - Protein C and S	- After two pregnancy losses: conform NVOG - After 3 pregnancy losses: - Antithrombin activity - APC-resistance, in case of abnormal value Factor V Leiden analysis. - APTT - Factor II mutation - Factor VIII - Fibrinogen - INR - Lupus APTT - Protein C-activity and antigen - PT - Thrombin time - Free proteins S-antigen	- Conform NVOG	- Conform NVOG - - Factor VIII not mentioned
Immunology/APS	- ACA IgG - ACA IgM - LAC	- Conform NVOG + - Anti β2-glycoprotein IgM - Anti β2-glycoprotein IgG - Value range given - Investigations performed 8 weeks after pregnancy loss	- Conform NVOG - Value range given - Investigations performed 12 weeks after pregnancy loss	- Conform NVOG + - Anti β2-glycoprotein IgM - Anti β2-glycoprotein IgG - No value range given - Investigations performed 12 weeks after pregnancy loss
Hyperhomocysteinemia	Random homocysteine	Random homocysteine	Random homocysteine	Random homocysteine

Endocrinology	Not indicated	TPO-antibodies in case of T4LIFE participation If patient history suggests abnormalities: Glucose, HbA1C, TSH, thyroxin (T4)	Thyroid functions in case of T4LIFE participation	TSH and TPO-antibodies In case of abnormal TSH values, Free T4 T4Life
Anatomy	No recommendation	3D ultrasound in second half of menstrual cycle in case of suspected anomaly, unless patient carried pregnancy until term. In case of suspected cavity anomaly: sonohysterography.	Transvaginal ultrasound	Ultrasound of uterus cavity In case of abnormalities, sonohysterography or hysteroscopy
Therapy				
Lifestyle recommendation	Weight loss Healthy diet Smoking cessation Vitamin supplementation not useful	Conform NVOG	Conform NVOG	Conform NVOG
APS	Aspirin 75-80 mg once daily preconceptionally until 36 weeks gestation together with LMWH subcutaneously once daily following detection of foetal heartbeat until delivery	Referral to local APS protocol	Conform NVOG	Conform NVOG

Balanced chromosomal abnormalities of the couple	IVF + preimplantation genetical testing	IVF and preimplantation genetical testing explanations Consulting clinical geneticist	Referral clinical geneticist Invasive diagnostic testing with regard to the low chance of live born children IVF + preimplantation genetic testing	Consult clinical geneticist
Septate uterus	Surgery not recommended	TRUST study	Surgery only in case of TRUST study participation	Ultrasound of uterus cavity In case of abnormalities, sonohysterography or hysteroscopy
Thrombophilia	No evidence for anticoagulatory drug treatments	ALIFE II study Treatment according to haematology protocol	ALIFE study Anticoagulatory treatment according to protocol	Referral to obstetrician
Hyperhomo-cysteinemia	Measurement of fasting total homocysteine level at least 12 weeks after pregnancy Measurement of fasting total homocysteine level at least 12 weeks after pregnancy Based on the results, vitamin supplementation can be recommended, after which homocysteine levels can be measured again after 6 weeks	Conform NVOG	Conform NVOG	Measurement of fasting total homocysteine level at least 12 weeks after pregnancy Measurement of fasting total homocysteine level at least 12 weeks after pregnancy Based on the results, vitamin supplementation can be recommended, after which homocysteine levels can be measured again after 6 weeks

M. Wilson	Not specified	Not specified	Not specified	Not specified
Unexplained RPL	Tender loving care: Smoking cessation Early pregnancy ultrasound Psychological support	Tender loving care: Approachable team Weekly ultrasound until 12 weeks gestation Psychological support	Not specified	Frequent ultrasound if desired
Success rate following pregnancy	Table	Table NVOG	Table NVOG	Table NVOG
Follow Up	Guidance throughout first trimester	Weekly ultrasound until 12 weeks gestation	Preconception consults for early ultrasound	Not specified
Research		ALIFE II, REMI, T4 life, TRUST	Not specified	ALIFE II, T4 life, TRUST
References		NVOG guideline and websites	Very thorough	None

	Non-academic hospital P1	Non-academic hospital P2	Non-academic hospital P3	Non-academic hospital P4
Terminology	Recurrent Pregnancy Loss	Habitual abortion or recurrent pregnancy loss	Habitual abortion	Recurrent Pregnancy Loss
Defining RPL	Conform NVOG	Habitual (>3 consecutive spontaneous abortions) Recurring (>2 consecutive spontaneous abortions)	Not specified (Webtool website Freya)	Conform NVOG
Risk factors	- Cytogenetic abnormalities - Family history - Maternal age - Obstetric history	- Deficiency of: - Antithrombin III, Protein C, Protein S, APC-resistance with or without Factor V Leiden mutation, spontaneous thrombocyte aggregation. - Balanced chromosomal abnormalities - Hyperhomo-cysteinemia - Maternal age - M. Wilson - Thrombophilia - Uterine abnormalities	- Not specified	- Anatomical abnormalities - Chromosomal abnormalities - Endocrine abnormalities - Hyperhomo-cysteinemia - Lifestyle - Unknown - Thrombophilia
Investigations				
General investigations	Conform NVOG	Karyotyping of both parents	Conform NVOG	Conform NVOG

Genetics	Conform NVOG	Karyotyping of both parents	Conform NVOG	Conform NVOG
Thrombophilia	Conform NVOG + APC-resistance	- APC-resistance - AT III - Factor II variant - Factor V Leiden - Factor VIII - Protein C and S - Thrombocyte count	Conform NVOG	Conform NVOG
Immunology/APS	- ACA - LAC - Measured 6 weeks after pregnancy loss	- ACA IgM and IgG - Anti β2-glycoproteïne I - Measured 8-10 weeks after pregnancy loss	- Conform NVOG - Measured 12 weeks after pregnancy loss (2x measured)	- ACA - Anti β2-glycoprotein antibodies - LAC - Measured 12 weeks after pregnancy loss (2x measured)
Hyperhomocysteinemia	Methionine load test	Fasting homocysteine	Fasting homocysteine	Homocysteine
Endocrinology	Not specified	Not specified	Not specified	Thyroid function and glucose (in case of complaints)
Anatomy	Not specified	Uterine ultrasound	Not specified	Uterine ultrasound or hysteroscopy

Therapy				
Lifestyle recommendation	Conform NVOG	Not specified	Weight loss	Weight loss Smoking cessation No excessive coffee and alcohol intake. Focus on medication use (NSAIDs), job and socio-economic status
APS	Conform NVOG	2x 5000 E heparin and 75 mg aspirin per day	Conform NVOG	Aspirin conform NVOG Once daily LMWH subcutaneously following positive pregnancy test Consider starting aspirin following a positive pregnancy test, especially in case of subfertility
Balanced chromosomal abnormalities of the couple	Not specified	Counselling, antenatal investigations in next pregnancy	Not specified	Preimplantation genetical testing according to risk of chromosomal abnormalities (NVOG table)
Septate uterus	Not specified	No evidence for surgical removal	Not specified	Surgical removal only in case of TRUST study participation
Thrombophilia	Not specified	In consultation with haematologist	In consultation with haematologist	Conform NVOG Vademecum Haematology

Hyperhomocysteinemia	Folic acid 5 mg and vitamin B6	Folic acid and/or vitamin B6	Conform NVOG - Homocysteine investigation three months after pregnancy not mentioned	Conform NVOG
M. Wilson	Penicillamine of zinc	Penicillamine	Not specified	Not specified
Unexplained RPL	General comment: treatment is only indicated when proven to reduce chance of a new pregnancy loss significantly	Not specified	Not specified	Psychosocial support Frequent ultrasound Lifestyle advice RPL outpatient clinic Participation in studies No anticoagulant therapy
Success rate following pregnancy	Not specified	Table NVOG	Table NVOG	Table NVOG
Follow Up	Not specified	Not specified	Not specified	No second line care, but increased risk of maternal and foetal complications (preeclampsia, placental abruption, PPROM, preterm birth, foetal growth restriction)
Research	Not specified	Not specified	Not specified	Promise, TRUST, REMI, ALIFE2, T4Life
References	NVOG guideline	NVOG guideline	Freya website NVOG guideline	Very thorough

REFERENCES

1. Aarts A, Clusters I. Diabetes Gravidarum. NTOG. 2014;127:467-72.
2. Nijkamp E, Aarts A. Hypertensieve aandoeningen in de zwangerschap. NTOG. 2015;128:506-12.
3. NVOG. Herhaalde Miskraam 2007 [08/06/2007:[Available from: www.nvog-documenten.nl/richtlijn/doc/download.php?id=750.
4. ACOG practice bulletin. Management of recurrent pregnancy loss. Number 24, February 2001. (Replaces Technical Bulletin Number 212, September 1995). American College of Obstetricians and Gynecologists. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2002;78(2):179-90.
5. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and sterility. 2010;93(4):1234-43.
6. Stirrat GM. Recurrent miscarriage. Lancet. 1990;336(8716):673-5.
7. Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. Fertility and sterility. 1996;66(1):24-9.
8. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Human reproduction (Oxford, England). 1999;14(11):2868-71.
9. Farquharson RG, Jauniaux E, Exalto N, Pregnancy ESIGfE. Updated and revised nomenclature for description of early pregnancy events. Human reproduction (Oxford, England). 2005;20(11):3008-11.
10. van Oppenraaij RHF, Goddijn M, Lok CAR, Exalto N. De jonge zwangerschap: revisie van de Nederlandse benamingen voor klinische en echoscopische bevindingen. NTvG. 2008;152:20-4.
11. Freya. Beslisprogramma Herhaalde miskramen 2016 [Available from: https://www.freya.nl/herhaalde-miskramenbeslisprogramma/.
12. European Association for Study of L. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85.
13. Bihl JH. The effect of pregnancy on hepatolenticular degeneration (Wilson's disease): Report of a case. American Journal of Obstetrics and Gynecology. 1959;78(6):1182-8.
14. Green P, Rubin L. Amenorrhea as a manifestation of chronic liver disease. American Journal of Obstetrics & Gynecology. 1959;78(1):141-6.
15. Sherwin AL, Beck IT, Mc KR. The course of Wilson's disease (hepatolenticular degeneration) during pregnancy and after delivery. Can Med Assoc J. 1960;83(4):160-3.
16. Studies-obsgyn.nl. T4-LIFE [Available from: http://www.studies-obsgyn.nl/T4-LIFE/page.asp?page_id=1333.

17. Empson M. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev. 2005;2.

18. Empson M, Lassere M, Craig JC, Scott JR. Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. Obstetrics and gynecology. 2002;99(1):135-44.

19. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ (Clinical research ed). 1997;314(7076):253-7.

20. Conceptrichtlijn Antitrombotisch Beleid 2015 [cited 2016 18 October 2016]. Available from: https://www.nvvc.nl/media/richtlijn/198/Richtlijn%20Antitrombotisch%20beleid_def.pdf.

21. Zhang T, Ye X, Zhu T, Xiao X, Liu Y, Wei X, et al. Antithrombotic Treatment for Recurrent Miscarriage: Bayesian Network Meta-Analysis and Systematic Review. Medicine (Baltimore). 2015;94(45):e1732.

22. Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ (Clinical research ed). 2003;327(7411):368.

23. Studies-obsgyn.nl. TRUST trial [cited 2016 18 October 2016]. Available from: http://www.studies-obsgyn.nl/trust/page.asp?page_id=669.

24. Studies-obsgyn.nl. ALIFE2 trial [cited 2016 18 October 2016]. Available from: http://www.studies-obsgyn.nl/ALIFE2/page.asp?page_id=1344.

25. Gezondheidsraad. Voedingsnormen: vitamine B6, foliumzuur en vitamine B12 [cited 2016 18 October 2016]. Available from: https://www.gezondheidsraad.nl/sites/default/files/03@04nr.pdf.

26. Roberts EA, Cox DW. Wilson disease. Baillieres Clin Gastroenterol. 1998;12(2):237-56.

27. Wiggelinkhuizen M, Tilanus ME, Bollen CW, Houwen RH. Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease. Aliment Pharmacol Ther. 2009;29(9):947-58.

28. Coomarasamy A. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 2015;373.