Review Article

Emerging role of Color Doppler in Infertility Management: A Public Health perspective

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ABSTRACT

Color Doppler is emerging as a valuable diagnostic imaging modality in the field of reproductive medicine, primarily infertility. Reproductive disorders, including infertility and spontaneous abortions/miscarriages, have emerged as major public health problem(s) worldwide. Color Doppler energy imaging is a high throughput technology based on the total integral of energy frequency spectrum. We extracted the most relevant articles (comprehensive reviews and original research articles) for inclusion in our review by performing a comprehensive literature search using the Pubmed (last accessed on 2015 April 28) scientific database. Color Doppler is a high-throughput, sophisticated imaging technique for the assessment of uterine anomalies, intrauterine pathology, tubal patency, polycystic ovaries, ovarian follicular monitoring, endometrial receptivity, failed and/or ectopic pregnancy, male infertility, and uterine, endometrial, and ovarian vascularity. Assessments of the uteroovarian pulsatility indices (PIs), resistance indices (RIs), and endometrial color signals are important determinants of *in vitro* fertilization (IVF) cycles and pregnancy rates. With our clinical/scientific research experience in the field of reproductive medicine, we strongly believe that an overall public health model needs to be designed in managing infertility patients; therefore, major issues such as cost-effectiveness and technical artifacts should be addressed so as to achieve an accurate clinical diagnosis, successful IVF outcome/pregnancy, and overall patient satisfaction in a clinical research setting. Simple, safe, efficient, and affordable diagnostic modalities should be incorporated at infertility clinics coupled with well-designed patient counseling sessions and community-based public health awareness campaigns conducted so as to reduce the morbidity and mortality rates associated with reproductive disorders.

Keywords: Color Doppler, cost-effectiveness, diagnosis, infertility, public health

INTRODUCTION

Our review highlights the emerging role of color Doppler as a valuable diagnostic imaging modality in the field of reproductive medicine, primarily infertility. Reproductive disorders, including infertility and spontaneous abortions/miscarriages, are emerging as major public health problem(s) worldwide; therefore, cost-effective screening strategies with observational follow-up intervention(s) and/or early identification of modifiable risk factors coupled with sophisticated clinical/molecular diagnostic modalities, for precise estimation of preventable proportion of miscarriages and/or infertility-related gynecologic pathologies, are essential to significantly prevent the increasing burden of reproductive disorders in susceptible women.[1] An interesting question arises as to whether it is possible to simplify the diagnostic procedures without

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substantially compromising the results and/or clinical diagnosis of complex gynecologic pathologies in infertility susceptible and/or asymptomatic individuals as well as symptomatic patient cohort in ethnically disparate populations, including North Indian cohort. Infertility is a major public health problem globally, including North India.[2,3] "Infertility" is defined as the inability to conceive following 12 months of regular unprotected sexual intercourse.[4] *Mycobacterium tuberculi* is the major etiological agent for female infertility;[5] altered anti-Müllerian hormone levels are associated with diminished ovarian reserve, predisposing women of reproductive age to adverse pregnancy outcomes.[6,7] Color Doppler energy imaging is a high throughput technology based on the total integral of energy frequency spectrum; it visualizes blood flow with the energy of moving reflectors and has the advantage of high sensitivity to slow blood flow, while being less dependent on angles and providing a less cluttered image.[8]

Search criteria for selection, extraction, and synthesis of data using scientific database(s)

The lead author of this review defined the search criteria for selection, extraction, and synthesis of the data after conducting an initial round of brainstorming session with her coauthors; few burning questions that need to be urgently addressed in the near future for cost-effective, safe and efficient management of infertility were identified by the lead author based on her extensive research experience, and these questions (denoted by "Q") were as follows:

Q1. How is infertility management different in terms of quality and cost-effectiveness from a public health perspective in India compared to the Western world?

Q2. What is the future of infertility-related, patient-centric clinical research in the years to come?

Q3. With the advent of high throughput, sophisticated, diagnostic techniques, including color Doppler imaging modality, infertility management has become relatively simple and safe; however, certain technical artifacts may lead to a possible misdiagnosis in certain cases. In this context, could missing an accurate diagnosis in the infertile Indian patient cohort mean a high price to pay, and could the patient be lost to follow-up?

Q4. Is there a consensus regarding the patient-counseling sessions organized at infertility clinics in India, primarily North India and/or in the state of Uttar Pradesh, as to whether the infertile couples should be counseled together and/or subjected to gender-specific, i.e., male- and female-only individualized counseling?

Q5. The entire cost of infertility treatment, from initial patient visits to subsequent follow-ups, including diagnostic procedures and assays is relatively high; in this scenario, can there be a "state-specific nodal center for infertility patients" to provide certain fixed level of financial support after a thorough assessment of the entire cost of treatment in Indian currency (INR). Furthermore, what are the constraints in setting up such a "nodal center for infertility patients?"

Q6. "Eliminating the blame game among infertile couples: Is it the husband or the wife who is responsible for childlessness?"

Q7. Are there ethical dilemmas and constraints including quality assurance and control in establishing, maintaining, and successfully managing an *in vitro* fertilization (IVF) laboratory in the 21st century? Moreover, how is the Indian scenario different from the Western world with regard to the ethical issues and/or constraints?

Q8. Compromising on embryo quality and culture media, including temperature variations and storage conditions, may eventually lead to ambiguous and/or contradictory IVF outcomes in ethnically disparate patient populations, e.g., North Indian, North American, and Danish patient cohorts. Could these issues be handled by ensuring routine laboratory inspections by a designated quality control/assurance scientific officer at the infertility clinic/medical center?

Q9. Micromanipulations and instrument-based experimental troubleshoots and/or artifacts in reproductive medicine research: How can IVF clinical experts as well as infertility scientists avoid erroneous and/or failed IVF results?

Thereafter, all the authors extracted a total of 32 most relevant articles related to color Doppler in reproductive disorders/infertility by performing a comprehensive literature search using the PubMed scientific database and accordingly included the selected articles (reviews and original research articles) in the present review; moreover, each of these 32 articles was thoroughly reviewed and the data/significant findings were assimilated for inclusion in our manuscript. The articles extracted were finally selected for inclusion in the manuscript based on the novelty of the research studies, assessment of objectives, methodologies (including color Doppler diagnostic modality), findings, outcomes, and overall clinical/public health impact.

Overview of color Doppler in reproductive disorders/infertility

Color Doppler is a high-throughput, sophisticated imaging technique for the assessment of uterine anomalies, intrauterine pathology, tubal patency, polycystic ovaries, ovarian follicular monitoring, endometrial receptivity, failed and/or ectopic pregnancy, male infertility, and uterine, endometrial, and ovarian vascularity.[9-14] Prehuman chorionic gonadotropin (hCG) three-dimensional power Doppler assessment of the follicle was implicated in improving pregnancy rates in intrauterine insemination cycles.[15] Three-dimensional volumetric reconstruction by the virtual organ computer-aided analysis (VOCAL) technique allows ovarian volume calculation, and automatic volume calculation software provides the follicular count and mean volumetric calculation;[16] furthermore, the life history of ovarian follicles involves endowment and maintenance, initial recruitment, maturation, atresia or cyclic recruitment, ovulation, and exhaustion.[17] Color Doppler producing ovarian vascular mapping allows the realization of a new functional approach of ovarian hyperstimulation syndrome (OHSS); local vascular factors, namely, ovarian angiogenesis and/or increase in capillary permeability released by hCG injection have a significant role in this syndrome.[18] Before induction, color doppler (CD) imaging allows the prediction of potential risk of hyperstimulation such as polycystic ovaries and spontaneous stromal hypervascularization; to monitor ovulation stimulation, to reduce the risk of multiple pregnancies, and to detect early hyperstimulation; to assess the severity of OHSS and predict complications such as ascites, hydrothorax, ovarian torsion as well as deep venous thrombosis. Ovarian multilobulated dysgerminoma with irregular internal

echogenicity but well-defined smooth lobulated contours may be examined by color/power Doppler;[19] enlarged ovary with diminished blood flow may be assessed by CD, thereby implicating the significance of CD in infertility management.[20] Clarifying the role of three-dimensional transvaginal sonography in reproductive medicine using an evidenced-based approach is indeed essential in recent times so as to reduce the increasing burden of reproductive disorders among ethnically disparate populations worldwide, including North India. Color Doppler imaging has emerged as a valuable clinical tool for understanding the complexities in *corpus luteum* efficiency and tubal pathologies; moreover, female infertility may be due to a broad spectrum of diseases involving the ovaries, uterus, or fallopian tubes. Hysterosalpingography is mainly used for the assessment of tubal patency and can also be used to guide tubal recanalization.[21] Abnormalities and/or vascular pathologies in uterine vessel(s) may be assessed by color or power Doppler ultrasound and expressed as downstream impedance to flow, thereby reflecting the actual blood flow to the endometrium although the major compartment of the uterus is the myometrium and there is collateral circulation between the uterine and ovarian vessels;[22] a three-dimensional dataset containing power Doppler information with relevant parameters may be acquired from the uterus and the VOCAL technique may be further used to define the myometrial-endometrial border and contour patterns. Subsequently, three-dimensional "wire" models of the endometrium may be generated; when VOCAL is used to calculate volume, a three-dimensional model is generated that may be rotated and further examined in its natural orientation, thereby demonstrating the fundal defect of an arcuate uterus while the actual anteflexion of the uterus may be appreciated in a different way, e.g., lateral view in the scan image. Two-dimensional Doppler flow indices and three-dimensional power Doppler indices provide an objective assessment of the blood flow toward endometrial and subendometrial regions, thereby evaluating endometrial receptivity and/or intraindividual variation in endometrial blood flow; the degree of power Doppler information and the difference in scan images may be quantifiable through the "histogram" facility, thereby demonstrating how vascularity is independent of morphometry and varies throughout the different phases of menstrual cycle, e.g., luteal/follicular phases.[22] Three indices of vascularity have been calculated for the endometrial model coupled with the mean gray value; the vascularization index (VI) reflects the degree of power Doppler information within the model and is considered as a percentage while the flow index (FI) and vascularization flow index (VFI) include information on the mean power Doppler signal intensity referenced against a scale (e.g., 0-100) to indicate the minimal and maximum ranges. Interestingly, Doppler blood flow measurement could be used to determine the optimal timing for the initiation of human menopausal gonadotropin (hMG) administration in patients undergoing ovarian stimulation after downregulation for IVF treatment; moreover, cervical pathologies may also be assessed using CD, for instance, a woman reporting with adenocarcinoma may be subjected to gray-scale transabdominal ultrasound and power Doppler imaging and the subsequent scans generated may be beneficial in defining cervical malignancy/lesion(s)/metastasis and intralesional vascularity.[23,24] Fractional moving blood volume (FMBV) in the uterine cervix may be estimated by power Doppler; the power Doppler box is positioned to include the entire cervix and the region of interest (ROI) is delineated by carefully following the contour patterns of the cervix; thereafter, the FMBV is calculated within the ROI.[25]

Recent advances

Color Doppler studies are immensely beneficial to the clinical/scientific community actively engaged in reproductive medicine research in the 21st century;[9-11,14] CD imaging has indeed proved to be a valuable diagnostic imaging modality during pregnancy and embryonic development(s), wherein an optimal blood supply toward the endometrium is essential for normal implantation.[1] A study by Dickey. suggested that pregnancy rate decreased when uterine pulsatility index (PI) was 3.3-3.5 and the uterine resistance index (RI) was 0.95.[26] Another study by Frieder *et al*. demonstrated that uterine PI had a high negative predictive value and sensitivity in the range of 88-100% and 96-100%, respectively, and a relatively higher range of positive predictive value and specificity (44-56% and 13-35%, respectively).[27] Ectopic and multiple pregnancies are emerging as one of the leading causes of morbidity and mortality in women of childbearing age and untreated, ectopic pregnancy can lead to massive hemorrhage and infertility, eventually resulting in death;[28] the advent of high-resolution color Doppler imaging is a boon for early prevention of pregnancy-related deaths in women worldwide. An elegant report highlighted the public health relevance of sophisticated uterine artery Doppler imaging as the possible valuable predictive factor governing pregnancy outcomes, including prediction/prevention of miscarriages in women of ethnically disparate populations;[1] in conjunction with serum assays for β-hCG, rapid and accurate diagnosis of pregnancy-related metabolic disorders is now routinely possible with CD imaging. Moreover, the locations of ectopic pregnancy may be ampullary/isthmic, infundibulum, fimbria, interstitial, intra-abdominal, ovarian, and cervical;[28] therefore, missing the accurate diagnosis may result in undesirable pregnancy-related complications and in critical circumstances, even death. A prospective study by Basir *et al*. investigated the blood flow parameters between cycles of the same women to assess whether the parameters predicting a successful pregnancy in a stimulation cycle could be used to determine the outcome of subsequent natural cycles.[29] Assessments of the uteroovarian PIs and RIs as well as endometrial color signals were performed by the study group in 58 IVF cycles and 40 natural cycles and the data demonstrated that in IVF cycles, the pregnancy rate (27%) was similar to that in frozen-thawed embryo transfer (FET) (28%) cycles; however, the uteroovarian PIs and RIs in IVF cycles were significantly lower than those in the natural cycles and there was a significant correlation between the uterine PI in stimulation cycles and that in natural cycles. Moreover, in IVF cycles, there was a significant decrease/decline in pregnancy rate when the uterine PI was >2.70 and the RI was >0.9, while no decline in pregnancy rate was observed in FET cycles. Also, conceptional FET cycles showed significantly higher uterine PI, uterine RI, and endometrial color signals compared with conceptional IVF cycles, thereby strongly implicating the pivotal role of CD imaging in infertility management and reproductive medicine research. The hemodynamic parameters in stimulation cycles are different from those in natural cycles and the precise values of these parameters in predicting pregnancy are also different. Intrascrotal abnormalities detected by CD imaging aid in the management of male infertility; vascular channels and reflux flow in varicocele, testicular microlithiasis, testicular tumors,

epididymal cyst, testicular cyst, and intrascrotal hemangioma may be accurately diagnosed using the modern, high-throughput Doppler imaging technique.[10]

The recent years have witnessed an upsurge of interest in color Doppler-based studies in understanding the complexities and/or pathologies associated with female infertility as well as male infertility. A recent study demonstrated the relevance of noninvasive translational cynomolgus monkey model for studying folliculogenesis and ovulation using color Doppler ultrasonography, thereby providing novel insights in the technology of assisted reproduction technique (ART); the study group measured follicular growth and ovulation in six cyclic cynomolgus monkeys using abdominal Doppler ultrasonography.[30] The mean follicular diameter on cycle day 6 (cycle day 0 = day of ovulation) was 3.7 mm that increased to 6.8 mm on cycle day 1; after ovulation, the mean diameter decreased to 4.6 mm, confirming ovulation, and the mean percentage of follicular size reduction after ovulation was 31%, thereby suggesting that ultrasonography in combination with color flow Doppler imaging is a useful, noninvasive, translational method to measure ovarian follicular growth and occurrence/timing of follicular rupture in cynomolgus monkeys. A prospective, case-controlled study evaluated the uterine arteries' blood flow before and after laparoscopic surgery in patients with ovarian endometriosis and its possible correlation with infertility.[31] The study enrolled 110 women of reproductive age (69 with ovarian endometriomas and scheduled for surgery, and 41 controls); transvaginal ultrasound with Doppler color flow was conducted to evaluate the RI of uterine arteries during the secretory phase, at enrollment (T0), and 3 months after laparoscopic surgery (T1). Moreover, at enrollment (T0) unilateral or bilateral flow alterations (RI $\geq$ 0.8) were observed in 38 out of 42 patients with ovarian endometriosis (90%), whereas in the control group only 17 women (41%) had Doppler alterations; the difference in uterine artery RI values between the cases and the controls was statistically significant ($P < 0.0001$) and a statistically significant improvement in uterine artery flow ($P < 0.0001$) was observed 3 months after surgical treatment of endometriosis. Interestingly, 19 patients with endometriosis (45%) were infertile before surgery and presented with uterine artery Doppler alterations at T0 while after surgery, the pregnancy rate was significantly higher in patients who presented with uterine artery flow normalization than in those with persistent uterine artery flow alterations ($P = 0.002$), thereby demonstrating a strong correlation between uterine artery flow abnormalities and suggesting that ovarian endometriosis and uterine artery flow improvement following surgery seem to increase the probabilities of achieving pregnancy.

Technical artifacts

Major issues such as cost-effectiveness and technical artifacts should be addressed so as to achieve an accurate clinical diagnosis, successful IVF outcome/pregnancy, and overall patient satisfaction in a clinical research setting. It is advisable that the scanner should focus on visualizing the ROI in the longitudinal axis in order to obtain the real three-dimensional volume of the target organ for high-quality image acquisition. However, this is not always possible, thereby causing occasional low quality scans that may lead to ambiguous data interpretation. Occasionally, the size of the scan angle may hinder the acquisition of the whole organ and subsequently affect the overall quality of the scan. Moreover, several user-defined field settings such as "transmitting frequency," which depends on the position and/or the depth of the color box, are automatically defined while some are rewritable by the user and programmable in the setup, namely, color gain, pulse repetition frequency, wall motion filter, line density, balance, and quality; gain artifacts arise from the delicate balance between having enough gain to visualize flow in the vessel but not having so much gain that the color signal bleeds into adjacent regions and in a few cases where there is inadequate gain, there may be flow but no color.[32]

Future perspectives

With our extensive clinical/scientific research experience in the field of reproductive medicine, we strongly believe that an overall community-based public health research model needs to be designed in managing infertility patients worldwide. Simple, safe, efficient, and affordable diagnostic modalities should be incorporated at infertility clinics/medical research centers coupled with well-designed/conducted patient counseling sessions and well-organized, community-based public health awareness campaigns so as to reduce the morbidity and mortality rates associated with reproductive disorders. The overall cost of treatment incurred by the infertile couples including initial patient visit(s) and subsequent biochemical/hormonal assays as well as diagnostic procedures, prescription drugs, IVF cycles, and follow-up visit(s), including stay at the hospital/medical center after embryo transfer/surgery, should be carefully evaluated at the time of initial counseling by a competent clinical research core group/team so as to have an eventual successful IVF outcome, thereby leading to patient satisfaction.

To summarize, future research and development efforts in the field of reproductive medicine are warranted to further provide more meaningful interpretation of the sophisticated color Doppler-based diagnostic imaging, thereby significantly increasing the success rates of IVF among infertile patients. Moreover, multicentric and/or multinational research and development (R and D) efforts may incorporate case-control/gene epidemiology, animal model(s), *in vitro* cell-based assays, and clinical trials for biomarker development utilizing genomics, proteomics, transcriptomics, and metabolomic approaches for efficient management of infertility patients of ethnically disparate populations worldwide, including our North Indian cohort with a relatively low socioeconomic background compared to the Western world.

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Conflicts of interest

S.P., G.K., A.B., and A.K. declare that they have no significant financial and/or other relationship(s) that might lead to a Conflicts of interest.

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